Study of inclusion complexes of valsartan with β-cyclodextrin and hydroxypropyl β-cyclodextrin

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Received 26 February 2009; revised 22 January 2010; accepted 25 January 2010

This study presents improvement in solubility and dissolution rate of valsartan (VAL) using β-cyclodextrin (βCD) and hydroxypropyl-β-cyclodextrin (HP-βCD). Formation and characterization of solid inclusion complexes were investigated by DSC, FTIR, SEM, 1H NMR and in-vitro dissolution studies. Preparation method influenced physical properties of binary mixtures. Inclusion complexes obtained by co-evaporation method showed higher in vitro drug dissolution rates.

Keywords: Co-evaporation method, Drug dissolution, Inclusion complexes

Introduction
Valsartan (VAL) is a potent, highly selective antagonist of angiotensin II AT1 receptor1,2 and lowers blood pressure in hypertensive patients. VAL is considered as a class II drug, a water insoluble, lipophilic and highly permeable compound3. Poor aqueous solubility and slow dissolution of VAL results in poor bioavailability4. This study presents improvement in solubility of VAL using β-cyclodextrin (βCD) and hydroxypropyl-β-cyclodextrin (HP-βCD) for better bioavailability.

Experimental
Materials
VAL was kindly supplied by Torrent (India); CAVASOL® W7 HP PHARMA (HP-βCD: MW = 1380 and DS = 0.6) was supplied by Wacker Fine Chemical Corporation (Germany); and βCD (MW = 1135) was supplied by Signet (India). These chemicals were used as received. All other chemicals and solvents were of analytical grade. Double distilled water was used throughout the study.

Apparatus
Differential Scanning Calorimetry (DSC) analysis was performed on METTLER TOLLEDO-DSC-822© (Japan) under dry nitrogen purge (50 ml/min) at a heating rate of 10°C/min over 30-200°C. Fourier Transform Infrared (FTIR) spectra of complexes were taken with Jasco-700 FTIR spectrophotometer (Shimadzu, Japan) between 4000-400 cm⁻¹ at resolution of 2 cm⁻¹. Surface morphology was visualized using Scanning Electron Microscope (JSM-5510, JEOL, USA). Proton nuclear magnetic resonance (¹H NMR) spectra of complexes of drug with cyclodextrins (CDs) were taken at 25°C by a Bruker DPX Digital Nuclear Magnetic Resonance Model (USA) operating at a proton frequency 400 MHz using DMSO [2.5 ppm from tetramethylsilane (TMS)] as a solvent.

Drug release was determined by evaluation of cumulative amount of drug released from drug-CD complexes using standard dissolution apparatus (6 station, VDA-6DR, USP type II–Veego Scientific, India) in 900 ml phosphate buffer pH 6.8 as dissolution media at 37.0 ± 0.5°C.

Phase Solubility Studies (PSS)
PSS were carried out in deionized water at 25°C5,6. An excess of VAL (50 mg) was added to distilled water (10 ml) containing increasing amounts of CDs (βCD and HP-βCD). Resulting suspensions were shaken for 48 h and then filtered through 0.45 μm Millipore filter, appropriately diluted and analyzed by UV-Vis spectrophotometer (SHIMADZU UV 1601) at 250 nm.

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Apparent stability constant \( (K_s) \) was calculated from phase solubility diagram as

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K_s = \frac{slope}{So(1 - slope)} \quad \text{...(1)}
\]

where, \( S_o \) is solubility of drug in absence of CDs.

**Preparation of Binary Mixtures**

All binary mixtures were prepared by drug and CDs (molar ratio, 1:1) based on results obtained from preliminary PSS. Physical mixtures (PM) were prepared by simple mixing of powders of both components in a mortar with pestle for 10 min. Kneaded (KN) product was obtained by adding small amounts of water to CD placed in mortar and mixing to obtain a homogenous paste. Then, saturated ethanolic solution of drug was added and mixture was kneaded for 3-4 h. During kneading process, few drops of water were introduced to maintain a suitable consistency. Resulting mass was dried in an oven at 45°C for 48 h and solid was finally ground. Co-evaporated (CE) product was obtained by adding alcoholic solution of VAL to aqueous solution of CD under sonication. Final solution was subjected to CE at 45°C and solid obtained was grounded.

**Results and Discussion**

**Phase Solubility Studies (PSS)**

Phase solubility diagrams obtained could be classified as \( A_1 \) type. Solubility of VAL increased with increasing concentration (0-6 mM) of \( \beta \)CD and HP-\( \beta \)CD. As slope of all these diagrams were < 1.0, it was possible to assess a 1:1 stoichiometry and calculate \( K_s \) of binary complexes. \( K_s \) of VAL-HP-\( \beta \)CD complex \((K_{1:1} = 667.92 \, \text{M}^{-1})\) was more than that of VAL-\( \beta \)CD complex \((K_{1:1} = 129.23 \, \text{M}^{-1})\). \( K_{1:1} \) showed that VAL formed more stable complexes with HP-\( \beta \)CD than \( \beta \)CD, may be due to extension of hydrophobic cavity without steric hindrance and provision of greater inclusion ability. At CD (conc., 6 mM), VAL solubility increased for \( \beta \)CD (47.14 %) and for HP-\( \beta \)CD (76.56 %).

**Differential Scanning Calorimetry (DSC)**

Thermal curve showed a melting endothermic peak at 115°C for drug. In thermal curves of PM of VAL and CDs (\( \beta \)CD and HP-\( \beta \)CD), endothermic peak for VAL, which is slightly broadened, indicates drug amorphization. Comparison of DSC curves of pure components and respective drug-carrier equimolar systems prepared by CE method revealed that endothermic peak of drug disappeared completely. Marked broadening and reduction in intensity of VAL DSC endotherm, when passing from PM up to its disappearance in co-evaporated complex, was indicative of complete drug amorphization and/or inclusion complexation as reported.

**Fourier Transform Infrared (FTIR) Spectroscopy**

FTIR spectra of inclusion complexes prepared by CE method exhibited some significant differences (shifts, broadening or attenuation) in characteristic bands revealing a modification of drug environment. Characteristic bands of VAL were two absorption bands at 1733.89 \( \text{cm}^{-1} \) (carboxyl carbonyl, CC) and 1602.74 \( \text{cm}^{-1} \) (amide carbonyl, AC). In case of \( \beta \)CD systems, absorption band for CC group of pure drug appeared unchanged in PM (1733.89 \( \text{cm}^{-1} \)), which was slightly shifted to 1732.92 \( \text{cm}^{-1} \) in case of inclusion complex. Absorption band for AC group was shifted to 1605.63 \( \text{cm}^{-1} \) in case of PM and to 1647.10 \( \text{cm}^{-1} \) in case of inclusion complex. In case of HP-\( \beta \)CD systems, absorption band for CC group of pure drug appeared unchanged in PM (1733.89 \( \text{cm}^{-1} \)), and slightly shifted to 1732.92 \( \text{cm}^{-1} \) in case of inclusion complex. Absorption band for AC group was shifted to 1605.63 \( \text{cm}^{-1} \) in case of PM and to 1637.45 \( \text{cm}^{-1} \) in case of inclusion complex.

In FTIR spectra, shift in AC band from 1602.63 \( \text{cm}^{-1} \) to 1647.10 \( \text{cm}^{-1} \) with \( \beta \)CD and 1637.45 \( \text{cm}^{-1} \) with HP-\( \beta \)CD in case of inclusion complexes were within the range for amide group (1695 \( \text{cm}^{-1} \) to 1600 \( \text{cm}^{-1} \)), indicating no chemical changes involved. This peak shifting towards lower frequency with change in intensity suggested change in environment of carbonyl group associated with amide moiety. Slight shifting of absorption band for carbonyl group of amide to a lower frequency can be attributed to breakdown of intermolecular hydrogen bonds associated with crystalline drug molecule and formation of hydrogen bonding of drug with CDs.

**Scanning Electron Microscopy (SEM)**

SEM analysis showed pure drug particles (5-30 \( \mu \)m) of irregular shapes and sizes (Fig. 1a). SEM of \( \alpha \)CD revealed a multifoliate structure with planar large crystal structure (Fig. 1b). As seen from SEM, complex exhibited a totally different crystalline structure, which is not comparable with morphology of pure drug, thus suggesting formation of drug - \( \beta \)CD complex (Fig. 1c). SEM of HP-\( \beta \)CD showed loss of sphericity, smooth
surface and reduced size of particles (Fig. 1d), which became inconspicuous following inclusion complexation with drug (Fig. 1e). Hence, changes in particle shape and size, although not much conclusive but suggesting an apparent interaction between drug and HP-βCD.

**Proton Nuclear Magnetic Resonance (1H NMR) Spectroscopy**

In CD molecule, hydrogen atoms are located in interior of cavity (H₃ and H₅) and outer surface of cavity (H₁, H₂, H₄, and H₆). When any guest molecule gets incorporated in CD cavity, hydrogen atoms located inside

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Fig. 1—Scanning electron images of: a) VAL; b) βCD; c) co evaporate of VAL with βCD; d) HP-βCD; and e) co evaporate of VAL with HP-βCD

Fig. 2—Dissolution profiles in phosphate buffer (pH 6.8, temp. 37.0 ± 0.5°C, n=6) of: VAL (♦); physical mixture of VAL [βCD (■)]; kneaded system of VAL [βCD (▲)]; co-evaporated system of VAL [βCD (×)]; physical mixture of VAL [HP-βCD (Δ)]; kneaded system of VAL [HP-βCD (◇)]; co-evaporated system of VAL [HP-βCD (+)]
cavity experience significant changes in δ ppm values. But in case of association of guest molecule with CD, hydrogen atoms on exterior surface show shifts in δ ppm values. Thus, a positive sign of ∆δ ppm shows a downfield displacement and a negative sign an upfield displacement. In case of βCD complexes, shift in δ ppm values were: H₁, 0.004; H₂, 0.027; H₃, -0.020; and H₄, -0.023. In case of HP-βCD complexes, shift in δ ppm values were: H₁, 0.005; H₂, 0.139; H₃, -0.017; and H₄, 0.006 (Table 1).

In ¹H NMR spectra of both complexes, magnitude of peak was lowered as compared to magnitude of peak for free drug, which also indicated that there were changes in environment of hydrogen of drug molecule. This suggested formation of complex between drug and CDs, and this interaction may be due to hydrogen bonding between drug and CDs as reported¹⁰.

In vitro Drug Release Study

In dissolution profiles of VAL, VAL-βCD and VAL-HP βCD (Fig. 2), VAL dissolved from binary systems was higher than that dissolved from plain drug. VAL showed 29.65 % release after 10 min with completion after 4 h. Binary systems prepared by CE displayed good dissolution performance after 10 min as follows: HP-βCD complex, complete release; and βCD complex, 93.58% release.

Amount of VAL dissolved from KN systems were slightly lower than CE systems although still higher than PM. Increased dissolution of VAL when physically mixed with CDs may be due to an improved wettability of drug particles at early stages of dissolution process as reported¹¹. Superior performances in dissolution testing exhibited by inclusion complexes prepared by CE method with βCD and HP-βCD may be attributed to formation of soluble complexes, superior wettability, amorphisation, reduction of particle size¹² and presence of highly hydrophilic carriers such as CDs¹³.

Conclusions

VAL could form 1:1 molar ratio inclusion complexes with βCD and HP-βCD by KN and CE methods. CE method enhanced solubility of VAL by 47.14 % with βCD and 76.56 % with HP-βCD with similar improvement in dissolution profiles. Therefore, a suitable dosage form incorporating these complexes might show improvement in oral bioavailability of VAL.

Acknowledgement

Authors thank Wacker Chemical Corporation (Germany) for providing free sample of CAVASOL® W7 HP PHARMA.

References


