Influence of levodropropizine and hydroxypropyl-β-cyclodextrin association on the physicochemical characteristics of levodropropizine loaded in hydroxypropyl-β-cyclodextrin microcontainers: Formulation and in vitro characterization

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Abstract

Background. Poorly water-soluble drugs do not dissolve well in aqueous-based gastrointestinal fluid; therefore, they are not well absorbed. Thus, employing a suitable solubility enhancing technique is necessary for such a drug. Drug/HP-β-CD complexation is a promising way to improve solubility and dissolution of a poorly water-soluble drug. Levodropropizine was used as a model drug in this study.

Objectives. The purpose of this research was to enhance the aqueous solubility and dissolution rate of levodropropizine by employing the inclusion complexation technique.

Material and methods. A microparticle formulation was prepared from levodropropizine and hydroxypropyl-β-cyclodextrin (HP-β-CD) in a 1:1 molar ratio through the spray-drying technique. The host-guest relationship between levodropropizine and HP-β-CD was also investigated using the molecular docking computational methodology. The aqueous solubility and dissolution rate of levodropropizine in formulations were assessed and compared with those of the drug alone. X-ray diffraction (XRD), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and Fourier transform infrared spectroscopy (FTIR) were applied for the solid-state characterization of the prepared samples.

Results. According to the research outcomes, the levodropropizine/HP-β-CD formulation had enhanced the aqueous solubility (351.12 ±13.26 vs 92.76 ±5.00 mg/mL) and dissolution rate (97.83 ±3.36 vs 3.12 ±1.76% in 10 min) of levodropropizine, compared to the plain drug powder. The levodropropizine/HP-β-CD formulation had converted the crystalline drug into its amorphous counterpart. Furthermore, no covalent interaction was found to exist between levodropropizine and HP-β-CD. The spray-dried particles were discrete. Each particle had a shriveled appearance.

Conclusions. The levodropropizine/HP-β-CD formulation is, therefore, recommended for the more effective administration of levodropropizine through the oral route.

Key words: dissolution rate, spray-drying, cyclodextrins, amorphous form, phase solubility

Introduction

Acute or chronic coughing is an indicator of various underlying respiratory illnesses. Acute coughing might be caused by a bacterial invasion in the upper respiratory tract during a common cold,[1] while other causes of chronic coughs include gastro-esophageal reflux disease (GERD), asthma, chronic bronchitis, or chronic obstructive pulmonary disease (COPD).[2] Irrespective of whether acute or chronic, coughing often accompanies several uncomfortable symptoms, such as nausea, vomiting, chest pain, headache, insomnia, or lethargy.[3] Antitussives offer much desired relief from the discomforts being caused by dry coughs.[4]

Antitussives either act centrally or peripherally. Centrally acting antitussives, such as codeine, cloperastine, morphine, dihydrocodeine, and dextromethorphan result in a number of adverse effects, including reduced alertness, somnolence, respiratory depression, and constipation.[5] Moreover, their frequent and prolonged use may result in patient tolerance and/or dependence. To circumvent such complications, treatment with peripherally acting antitussives is considered more favorable.

Levodropropizine [(2S) -3-(4-Phenylpiperazin-1-yl) propane-1, 2-diol], an isomer of dropropizine (Fig. 1A), is a peripherally acting cough suppressant that is used in the management of dry coughs, pertaining to various pulmonary morbidities.[6] Its peripheral action involves the inhibition of cough reflexes by the modulation of sensitive C-fibre activity.[7] Levodropropizine is only slightly soluble in water.[8]

Levodropropizine is as effective as dropropizine in relieving cough. Moreover, it has lower risk of somnolence than dropropizine.[9] Levodropropizine is only slightly water-soluble.[10] For improving the potency, absorption and efficacy of a slightly soluble drug, an aqueous solubility improving technique can be adopted.[11] Various techniques have been employed for improving the aqueous solubility and dissolution rates of slightly soluble drugs.[12–15]

The oral route is the most preferred way of drug administration, owing to its higher safety and the convenience of such administration.[16] An orally administered drug achieves its intended pharmacological effects when it is traversed from the gastrointestinal tract, enters the general blood circulation and reaches the target site of action. The dissolution of a drug in the aqueous gastrointestinal fluid is essential for traversing the gastrointestinal–blood barrier as a solid drug cannot cross cell membranes. Thus, on the basis of the aqueous solubility and permeation across cell membranes, Biopharmaceutics Classification System (BCS) has placed drugs under 4 classes.[17] Poorly water soluble drugs are included in BCS class II. Such a drug is insufficiently absorbed from the gastrointestinal tract (GIT)[18]; therefore its oral bioavailability is low. Thus, high doses are required to cross the minimum effective concentration (MEC) level in the blood, as concentration below MEC of a drug cannot illicit the specific receptors to produce particular pharmacological effects associated with it. Moreover, high doses can result in local toxicity in the GIT. Accordingly, aqueous solubility-enhancing techniques are employed for improving the potency, absorption and efficacy of insoluble or slightly soluble drugs.[19]

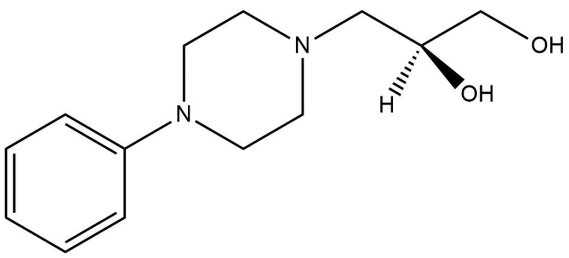

Fig. 1A. Structural formula of levodropropizine (ChemDraw Ultra 12.0)

Several techniques have been adopted for enhancing the aqueous solubility, dissolution rate, absorption, bioavailability, potency, and efficacy of various slightly water soluble drugs.[13,14] Among others, the inclusion complexation technique has been successfully used for augmenting the aqueous solubility and dissolution rate of slightly soluble drugs.[12] Cyclodextrins, such as hydroxypropyl-β-cyclodextrin (HP-β-CD), are hydrophilic oligomeric matrices that can improve the aqueous solubility and dissolution rate of a slightly soluble drug by converting the crystalline form of the drug into its amorphous counterpart.[20] A cyclodextrin molecule possesses a hydrophilic exterior and a lipophilic inner cavity.[21] A poorly water soluble drug molecule resides within the inner cavity during complex formation.[22] Although several weak intermolecular forces may exist between the drug and the cyclodextrin molecules,[23] new covalent bonds are not formed and the pre-existing covalent bonds are not weakened during complex formation.[24,25] Amongst other cyclodextrins, hydroxypropyl-β-cyclodextrin (HP-β-CD) (Fig. 1B) possesses a greater ability to house or accommodate various insoluble, or slightly soluble, drug molecules.[26] Because the cyclodextrins cannot be absorbed from the gastrointestinal tract, they are considered non-toxic when administered orally.[27] Toxicological investigations have proven that HP-β-CD is absolutely non-toxic.[28]

Thus, in the present research, the solubility and dissolution rate of levodropropizine were improved using HP-β-CD in order to increase its potency and oral absorption, and decrease possible local toxicity associated with high doses.[11] A microparticulated sample of levodropropizine and HP-β-CD, in a 1:1 molar ratio,[29] was prepared through the solvent evaporation method, using the spray-drying technique.[30] Spray-drying is considered to be a promising technique for the preparation of a drug/HP-β-CD formulation, allowing the amorphous form of the drug to be contained, due to the rapid evaporation of the solvent.[30] The host–guest relationship between levodropropizine and HP-β-CD was also studied by employing the mo-

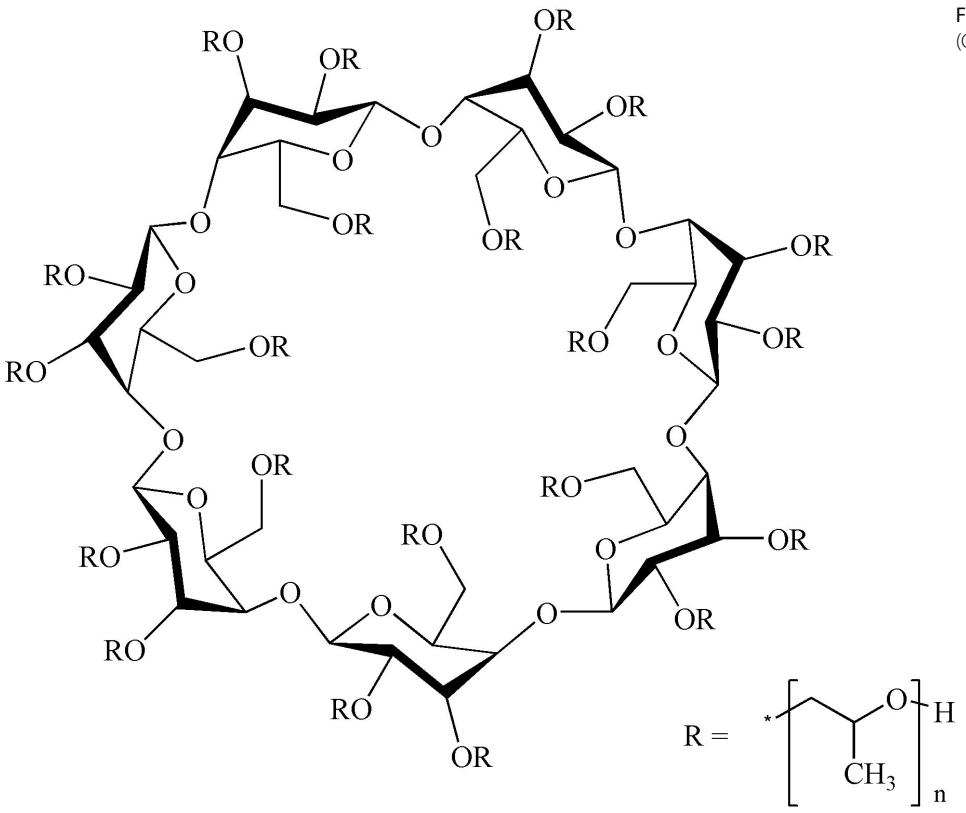

Fig. 1B. Structural formula of HP-β-CD (ChemDraw Ultra 12.0)

lecular docking computational methodology. The aqueous solubility and dissolution rate of levodropropizine were determined and compared with those of the drug alone. X-ray diffractometery (XRD), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and Fourier transform infrared spectroscopy (FTIR) were employed for the solid-state characterization of the preparation.

Material and methods

Material

Hydroxypropyl-β-cyclodextrin (HP-β-CD) was obtained from Sigma-Aldrich Co. (St. Louis, USA). Levodropropizine was procured from Jinan Chenghui-Shuangda Chemical Co. (Jinan, China). All other chemicals were of the reagent grade.

Phase solubility study

Various concentrations of HP-β-CD were prepared by dissolving solid HP-β-CD in water (0.0357 M, 0.0715 M, 0.143 M, 0.214 M, and 0.286 M).The solubility of levodropropizine in each of these aqueous solutions of HP-β-CD was determined using the Higuchi and Connors phase solubility method.[29] An excess amount of levodropropizine was transferred into 1 mL of each aqueous solution of HP-β-CD in 2 mL microtubes and vortexed for 1 min. These tubes were then fixed to an agitator in a water bath (25°C) and the samples mechanically shaken (250 rpm) for 2 days. After centrifugation at ×5,000 for 2 min, the supernatant of each sample was carefully withdrawn by means of 1 mL syringes, filtered and adequately diluted. These dilutions (2 mL) were analyzed on a HALO DB-20 UV-visible spectrophotometer (Dynamica Scientific Ltd., Clayton, Australia) at 240 nm. The complexation efficiency (E_C) and stability constant (K_S) were determined with the following formulas: $E_C = m/1–m$ and $K_S = E_C/S_0$, where m is the slope of the straight line of the phase solubility graph and S_0 is the intrinsic solubility or solubility of levodropropizine in water in the absence of HP-β-CD.

Computational methodology for molecular docking

In order to rationalize the achieved results from the phase solubility study, a molecular docking study for the levodropropizine/HP-β-CD formulation was conducted using the Molecular Operating Environment (MOE) 2015.10 software (Chemical Computing Group, Montreal, Canada). The 3D structure of β-CD was retrieved from the RCSB Protein Data Bank (PDB ID code: 1jl8) and used as a structural template for building the final structure of HP-β-CD by adjusting the corresponding functional group with the Sybyl-X1.3 SKETCH module. Levodropropizine was constructed by also using the SKETCH module, which was employed in Sybyl-X1.3.

Its potential energy was minimalized by means of a Tripos force field and Gasteigere-Huckel atomic charge, which had a distance-dependent dielectric function and a convergence criterion of 0.001 kcal/(mol·Å). All parameters were kept at default values for molecular docking in MOE. The best binding conformations of ligand in oligomer were ranked based upon their docking scores. In conclusion, the best energy model was selected and graphically analyzed.

Preparation of the levodropropizine/HP-β-CD formulation

Levodropropizine and HP-β-CD in a 1:1 molar ratio were dissolved in 90% ethanol to prepare an absolutely transparent solution. Subsequently, the solution was subjected to spray-drying using a mini spray dryer (Büchi B-290, Labortechnik AG Co., Flawil, Switzerland). The feed rate, spraying air pressure, internal diameter of the spraying nozzle, inlet temperature, outlet temperature, aspirator setting, and aspiration pressure in the filter vessel were 3 mL/min, 4 kg/cm^2, 0.7 mm, 95°C, 60°C, 90% and –45 mbar, respectively. The dried formulation was accumulated in the product collector.

Levodropropizine content determination

The formulation, equivalent to 10 mg of levodropropizine, was dissolved in 30 mL of ethanol in a 100 mL volumetric flask and the volume amounted to 100 mL with ethanol. The theoretical concentration of the solution was 100 µg/mL. One milliliter of this clear solution was filtered and adequately diluted. The dilution (2 mL) was analyzed on a HALO DB-20 UV-visible spectrophotometer at 240 nm. The test was performed in triplicate. The levodropropizine content was determined, using the formula: $L_C = L_A/L_T \times 100$, where, L_C is the levodropropizine content [%], L_A is the actual concentration of levodropropizine [µg/mL] as determined on the UV-visible spectrophotometer, and L_T is the theoretical levodropropizine concentration [µg/mL].

Aqueous solubility test

To determine the effect of the levodropropizine/HP-β-CD formulation on the aqueous solubility of the drug, a sufficient quantity of the formulation was transferred into 1 mL of distilled water in a 2 mL microtube and vortexed for 1 min. Each tube was then secured to a mechanical shaker in a water bath (25°C) and agitated (100 rpm) for 5 days.[30] After centrifugation at ×5000 for 2 min, the supernatant of each sample was carefully withdrawn by means of 1 mL syringes, filtered using syringe filters and adequately diluted. Each dilution (2 mL) was assayed on a HALO DB-20 UV-visible spectrophotometer at 240 nm.

Dissolution test

Dissolution studies were performed on both the active ingredient alone and on the formulation. Quantities of the formulation and of the drug powder, equivalent to 30 mg of levodropropizine, were enclosed in Spectra/Por® dialysis pouches (Spectrum Labs, Rancho Dominguez, USA) and placed in the baskets of a Vision® Classic 6™ USP dissolution tester I (Hanson Research Co., Los Angeles, USA). Each rotating basket (100 rpm) was then immersed in 900 mL of a 2% (w/v) aqueous solution of Polysorbate 80 in round bottom dissolution vessels.[31] The dissolution medium temperature was maintained at 37 ±0.5°C by the surrounding water bath. One milliliter of dissolution medium was sampled from each dissolution vessel at each of the following time intervals: 5 min, 10 min, 15 min, 20 min and 30 min. Each sample was filtered using syringe filters and adequately diluted. The levodropropizine in each dilution (2 mL) was quantified on a HALO DB-20 UV-visible spectrophotometer at 240 nm.

Crystallinity test

The intensity of crystallinity of the levodropropizine plain powder and the HP-β-CD separately, of a physical mixture of the 2 components, and of the levodropropizine/HP-β-CD formulation were examined by employing XRD and DSC techniques. The physical mixture was prepared by thoroughly triturating levodropropizine and HP-β-CD in a 1:1 molar ratio, using a pestle and mortar. The samples were scanned on a D/MAX-2500 PC X-ray diffractometer (Rigaku Corporation, Tokyo, Japan), equipped with a Cu $K\alpha_1$ monochromatic radiator. Each sample, mounted on the sample plate, was scanned between 10–80°, using a step-size, scanning mode, scanning speed, current and voltage of 0.02°/s, 2θ, 5°/min, 100 mA, and 40 kV, respectively.[30] A DSC Q20 differential scanning calorimeter (TA Instruments, New Castle, USA) was used for DSC analysis in the range of 30–130°C. Each sample, completely sealed in an aluminum crucible, was heated at a rate of 5°C/min under a nitrogen supply of 30 cm^3/min.

Morphological features study

The shape, size and surface physiognomies of the particulate samples were perused, using an S-4800 scanning electron microscope (Hitachi, Tokyo, Japan). The samples were affixed onto the exposed surface of a double-sided adhesive tape, already clung onto the metallic disc with its one side. The samples were then coated with platinum under 7×10^{-3} mbar pressure, using a K575X EMI Teck Ion Sputter to facilitate electrical conduction for imaging. The current and turbo speed were 25 mA and 100%, respectively.

Fourier transform infrared spectroscopy spectroscopic analysis

For FTIR spectroscopic analysis, a Nicolet-6700 FTIR spectrophotometer (Nicolet Instrument Corporation, Madison, USA) was used. A minute quantity of each sample was transferred into the fixed crucible, or sample slot, located exactly below the compression tip. Before scanning in the range of 600–4000 cm^{-1}, the hollow pin, bearing the scanning lens inside, was adjusted downwards onto the sample for compression between the sample slot and the compression tip.

Results and discussion

Among the cyclodextrins, HP-β-CD possesses a higher affinity for water-insoluble or slightly water-soluble, molecules and was thus chosen for the inclusion complex formation during this research.[26] Since the exterior of the HP-β-CD molecule is hydrophilic, while its inner cavity is lipophilic, it can accommodate the slightly water-soluble levodropropizine molecule within its cavity, where an inclusion complex is formed to possibly improve the aqueous solubility of the drug.[26]

Total degree of substitution (TDS) is defined as the average number of substituted moieties per cyclodextrin molecule.[32] The average molar degree of substitution (MS) is defined as the average number of moles of the substituting agent per mole of glucopyranose.[24,33] The degree of substitution is defined as the average number of substituted hydroxyls per glucopyranose of the cyclodextrin molecule.[34] HP-β-CD used in this research had a molecular weight (MW) of 1400 Da. When no additional reactive moieties are generated as a consequence of substitution reaction, the MS is equal to DS. No net gain or loss of any atom takes place in the hydroxypropylation reaction; therefore, the molecular formula of HP-β-CD can be expressed as $C_{42}H_{70}O_{35} + (C_3H_6O)_n$, where *n* is the number of moles of propylene oxide (substituent of hydroxypropyl) added. Thus, MW = 58.08 × (T.D.S.) + 1135, where 1135 is molecular weight of betadex ($C_{42}H_{70}O_{35}$) and 58.08 is the molecular weight of propylene oxide (C_3H_6O).[32] As the β-cyclodextrin molecule consists of seven glucopyranose units, TDS = 7 × MS. Therefore, MW = 406.56 × (M.S.) + 1135. From this discussion, TDS and MS in our study were 4.56 and 0.65, respectively. Moreover, DS was 0.65.[35]

For determining the apposite composition of the levodropropizine/HP-β-CD formulation, the Higuchi and Connors phase solubility study model was employed.[29] The straight line ($r^2 = 0.9999$) graph obtained during this study is demonstrated in Fig. 2. From the graph, the slope of the line was determined at 576.79, while the y-intercept, representing the solubility of the drug in the absence of HP-β-CD, was 394.47 M. The complexation

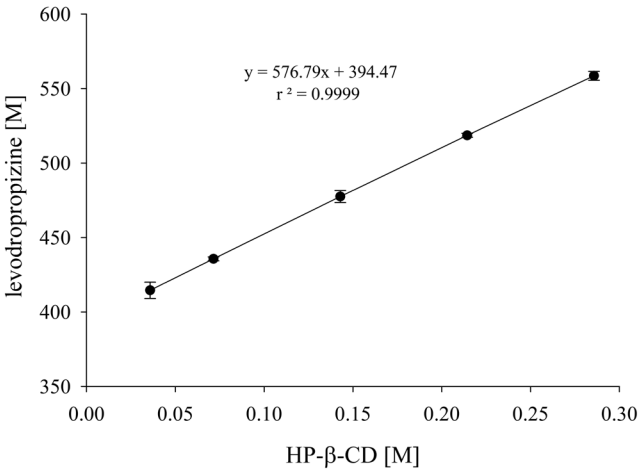

Fig. 2. The levodropropizine/HP-β-CD phase solubility diagram acquired in water at 25°C. Each value represents the mean ±SD; (n = 3)

efficiency (E_C) and stability constant (K_S) were 1.0017 and 2.539×10^{-3} M^{-1}, respectively. According to this phase solubility model, therefore, levodropropizine and HP-β-CD were prepared in a 1:1 molar ratio for this formulation.[29]

The most likely molecular model for the inclusion complex of levodropropizine and HP-β-CD, depicting the possible interaction of the drug molecule with HP-β-CD cavity, is shown in Fig. 3. These results indicate that levodropropizine interacted with HP-β-CD in a 1:1 molar ratio, and thus had the best stability constant (K_S) and complexation efficiency (E_C), which was in agreement with the conclusions of the Higuchi and Connors phase solubility study. Furthermore, with regards to the docking with HP-β-CD, the binding energy was –6.3 kcal/mol. Graphical analyses of the docking results revealed that the phenylpiperazine moiety of levodropropizine was retained at the margin of cavity, while the propane-1,2-diol moiety forming hydrogen bonds to the secondary hydroxyls along the rims of HP-β-CD had an average distance of 2.93Å (Fig. 3).

The spray-drying technique, in conjunction with the solvent evaporation method, is considered the best way to prepare formulations with HP-β-CD.[30] In this method, since the drug and HP-β-CD are completely dissolved in a solvent prior to subjecting them to spray-drying, the drug content is the highest in the solid product, owing to homogeneous intermingling at the molecular level. In this study, the drug content in the solid levodropropizine/HP-β-CD formulation was 100.26 ±1.64% (n = 3).

HP-β-CD has reportedly been successfully used for enhancing the aqueous solubilities and dissolution rates of various drugs, such as tacrolimus,[36] fenofibrate,[30] azithromycin,[37] nimesulide and meloxicam,[38] and apigenin.[37] In this study, the aqueous solubility and dissolution rate of levodropropizine were improved by the levodropropizine/HP-β-CD formulation, compared to those of the levodropropizine powder alone. The improvement

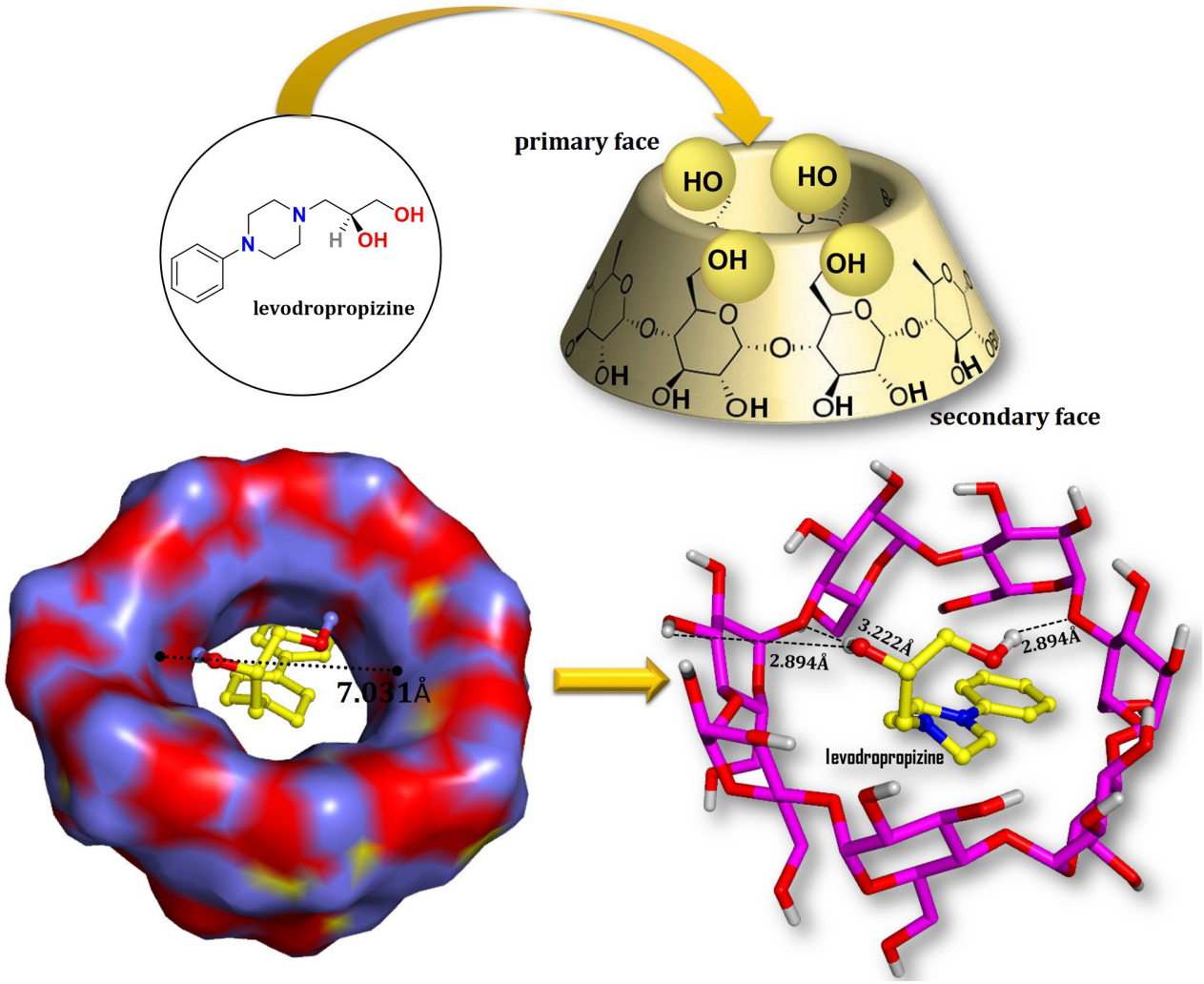

Fig. 3. Binding mode of levodropropizine (yellow ball-sticks) into HP-β-CD (magenta sticks). Possible H-bonds are shown with doted lines

in the aqueous solubility of levodropropizine in formulation was 351.12 ±13.26 vs 92.76 ±5.00 mg/mL, while the enhancement of its dissolution rate was 97.83 ±3.36 vs 3.12 ±1.76% in 10 min (Fig. 4).

The XRD patterns of the test samples are illustrated in Fig. 5. The levodropropizine powder gave typical sharp crystalline peaks in the 10–30° range (Fig. 5A). HP-β-CD did not generate any sharp peaks, suggesting its amorphous nature (Fig. 5B). Levodropropizine-related distinguishing peaks were visible in the XRD pattern of the physical mixture as well (Fig. 5C). These peaks were, however, absent in the diffractogram of the levodropropizine/HP-β-CD formulation (Fig. 5D). This suggested that levodropropizine had changed from its crystalline state into its amorphous state in the spray-dried levodropropizine/HP-β-CD formulation during preparation through the solvent evaporation method.[30]

Likewise, the DSC results were in harmony with the XRD results. The DSC thermograms are shown in Fig. 6. A deep endotherm was present at about 103°C for the levodropropizine powder, suggesting the melting point of the crystals (Fig. 6A). Although no peak appeared

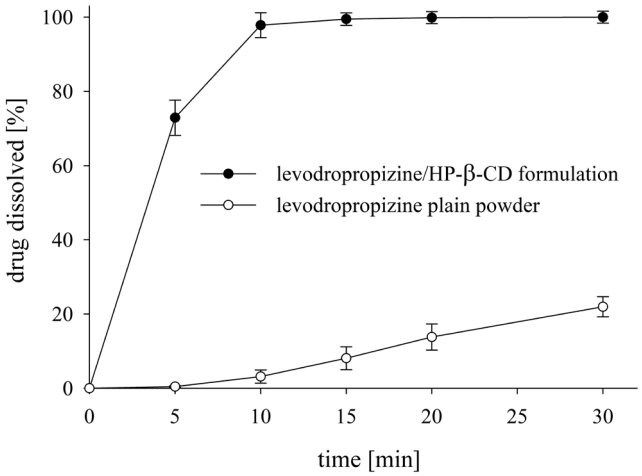

Fig. 4. Effect of levodropropizine/HP-β-CD formulation on the dissolution of the drug compared to plain levodropropizine. Each value of dissolution represents the mean ±SD; (n = 6); $p < 0.05$ at all points

in the HP-β-CD test results, confirming its amorphous nature, an endothermic sliding behavior in the curve was observed, owing to the escape of loosely bound mois-

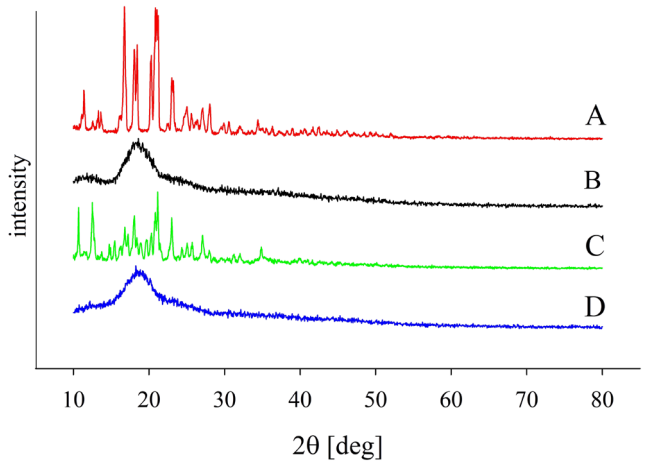

Fig. 5. XRD patterns: (A), levodropropizine; (B), HP-β-CD; (C), physical mixture; (D), levodropropizine/HP-β-CD formulation

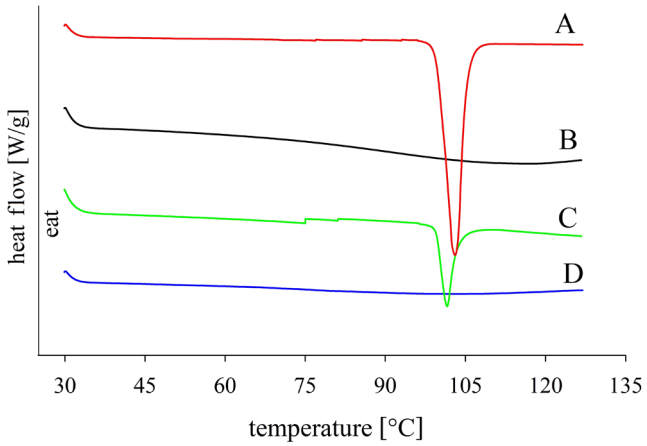

Fig. 6. DSC thermograms: (A), levodropropizine; (B), HP-β-CD; (C), physical mixture; (D), levodropropizine/HP-β-CD formulation

ture from HP-β-CD (Fig. 6B).[30,39] A sharp endotherm, at the melting point of levodropropizine, was also recorded for the physical mixture (Fig. 6C). Neither a sharp endotherm nor a downward curve behavior appeared in the thermogram of the levodropropizine/HP-β-CD formulation (Fig. 6D). This confirmed that the crystalline levodropropizine had changed into its amorphous form and that the formulation had been completely dry after spray-drying.

The scanning electron micrographs are shown in Fig. 7. Levodropropizine exhibited crystalline structures with irregular shapes and surfaces (Fig. 7A). The HP-β-CD particles were of irregular shapes, rough surfaces and large in size (Fig. 7B). The spray-dried particles of the levodropropizine/HP-β-CD formulation were discrete (Fig. 7C). Each particle, about ≤2 μm in size, furnished an elliptical shape and wrinkled surface (Fig. 7C inset).

The FTIR spectra are displayed in Fig. 8. Levodropropizine gave its distinctive peaks in the fingerprint region at 654 cm^{-1}, 740 cm^{-1}, 802 cm^{-1}, 870 cm^{-1}, 920 cm^{-1}, 996 cm^{-1}, 1049 cm^{-1}, 1097 cm^{-1}, 1142 cm^{-1} and

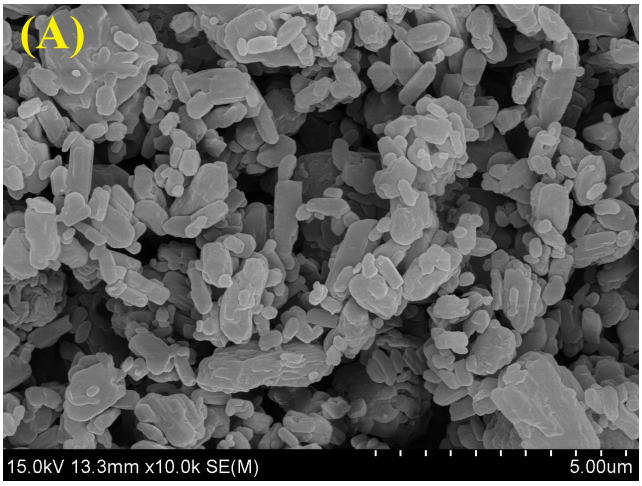

Fig. 7A. SEM image of levodropropizine (×10,000)

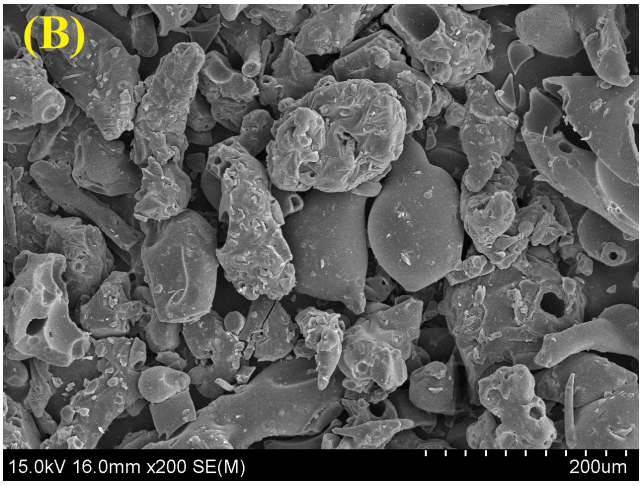

Fig. 7B. SEM image of HP-β-CD (×200)

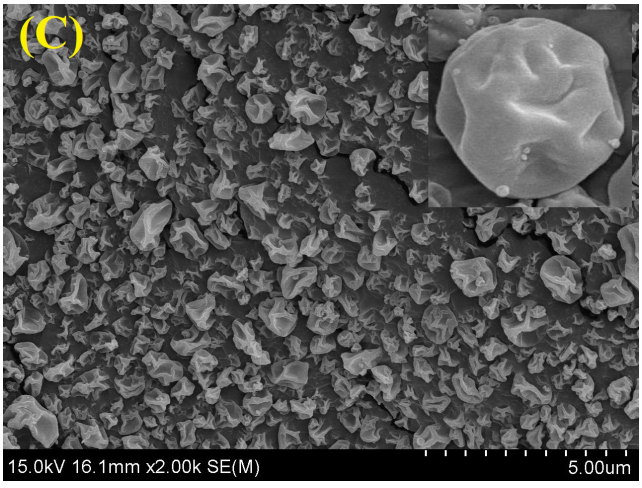

Fig. 7C. SEM image of levodropropizine/HP-β-CD formulation (×2,000)

1387 cm^{-1} (Fig. 8A). These characteristic peaks appeared in both the spectra of the physical mixture (Fig. 8C) and of the spray-dried levodropropizine/HP-β-CD formulation (Fig. 8D). Compared to the physical mixture,

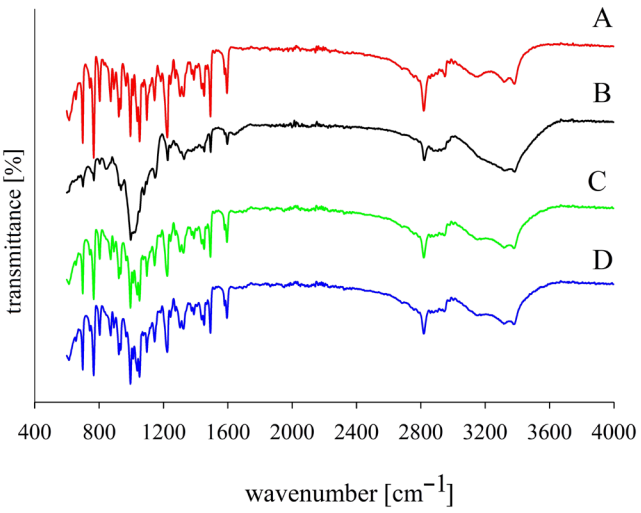

Fig. 8. FTIR spectra: (A), levodropropizine; (B), HP-β-CD; (C), physical mixture; (D), levodropropizine/HP-β-CD formulation

there was no shifting, nor the disappearance of existing peaks, nor the emergence of new peaks in the spectrum of the levodropropizine/HP-β-CD formulation. Moreover, the spectrum of the physical mixture overlaid that of the levodropropizine/HP-β-CD formulation (Fig. 8CD). This suggested that no covalent bonding had existed between levodropropizine and HP-β-CD during the inclusion complex formation process.[40]

From the above discussion, it could be established that the levodropropizine/HP-β-CD formulation had indeed improved the aqueous solubility and dissolution rate of levodropropizine, owing to the following factors: (i) homogeneity and closeness between the levodropropizine and HP-β-CD molecules, which had facilitated wetting,[36] (ii) alteration of the crystalline levodropropizine into its amorphous form,[41] and (iii) reduction in the particle-size of the active ingredient, offering an increased surface area available for dissolution.[42]

Conclusions

The levodropropizine/HP-β-CD formulation (1:1 molar ratio) had increased the aqueous solubility (351.12 ±13.26 vs 92.76 ±5.00 mg/mL) and dissolution rate (97.83 ±3.36 vs 3.12 ±1.76% in 10 min) of levodropropizine, compared to the drug alone. This improvement can be ascribed to (i) the presence of HP-β-CD, which expedited wetting, (ii) alteration of the crystalline levodropropizine into its amorphous state, and (iii) a decrease in the particle-size of the active ingredient, resulting in its increased surface area. Accordingly, this formulation might be a prospective delivery system for administering levodropropizine through the oral route, with improved solubility and dissolution.

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