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Preparation of olanzapine and methyl-β-cyclodextrin complexes using a single-step, organic solvent-free supercritical fluid process: An approach to enhance the solubility and dissolution properties

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ABSTRACT

The purpose of this study was to evaluate a single-step, organic solvent-free supercritical fluid process for the preparation of olanzapine-methyl-β-cyclodextrin complexes with an express goal to enhance the dissolution properties of olanzapine. The complexes were prepared by supercritical carbon dioxide processing, co-evaporation, freeze drying and physical mixing. The prepared complexes were then analysed by differential scanning calorimetry, X-ray powder diffraction, scanning electron microscopy, solubility and dissolution studies. Computational molecular docking studies were performed to study the formation of molecular inclusion complexation of olanzapine with methyl-β-cyclodextrin. All the binary mixtures of olanzapine with methyl-β-cyclodextrin, except physical mixture, exhibited a faster and greater extent of drug dissolution than the drug alone. Products obtained by the supercritical carbon dioxide processing method exhibited the highest apparent drug dissolution. The characterisation by different analytical techniques suggests complete complexation or amorphisation of olanzapine and methyl-β-cyclodextrin complexes prepared by supercritical carbon dioxide processing method. Therefore, organic solvent-free supercritical carbon dioxide processing method proved to be novel and efficient for the preparation of solid inclusion complexes of olanzapine with methyl-β-cyclodextrin. The preliminary data also suggests that the complexes of olanzapine with methyl-β-cyclodextrin will lead to better therapeutic efficacy due to better solubility and dissolution properties.

1. Introduction

Olanzapine is a second-generation atypical neuroleptic drug approved by the Food and Drug Administration as a first-line therapy for the treatment of schizophrenia and mania associated with bipolar disorder (Abdelbary and Tadros, 2013). It suffers from poor aqueous solubility (12–44 μg mL^{-1}) and a low dissolution rate leading to an erratic bioavailability (Kulkarni et al., 2010; Dixit et al., 2011; Raman et al., 2013). Moreover, the drug undergoes extensive hepatic first-pass metabolism and is required in high doses (Sood et al., 2013).

Several approaches have been reported to enhance the solubility and dissolution rate of olanzapine, *e.g.* solid-dispersions (Krishnamoorthy et al., 2011), nano-emulsions (Raman et al., 2013), solid-lipid nanoparticles (Sood et al., 2013), freeze dried tablets (Dixit et al., 2011) and inclusion complexation with cyclodextrins (Kulkarni et al., 2010; de Freitas et al., 2012).

Cyclodextrins, also known as cyclomaltoses, cycloamyloses and Schardinger dextrins, are macrocyclic oligomers of α-D-glucose with a hydrophilic exterior and a relatively non polar central cavity (Appel et al., 2012; Kfoury et al., 2014, 2015; Rudrangi et al., 2015). Cyclodextrins can form inclusion complexes by taking up the entire or a part of lipophilic drug molecule in its hydrophobic interior cavity (Loftsson and Duchêne, 2007; Salústio et al., 2009). Through formation of inclusion complexes, cyclodextrins are known to enhance the aqueous solubility and dissolution rate of poorly soluble drugs (Trapani et al., 2000; Pose-Vilarnovo et al., 2001; Latrofa et al., 2001; Jain and Adeyeye, 2001; Riekes et al., 2010).

The study published by de Freitas et al. (2012) reported that olanzapine and methyl-β-cyclodextrin (Me-β-CD) complexes

Abbreviations: Me-β-CD, methyl-β-cyclodextrin; SC-CO_2, supercritical carbon dioxide; SEM, scanning electron microscopy; DSC, differential scanning calorimetry; XRPD, X-ray powder diffraction; DP, percent drug dissolved; DE, dissolution efficiency.

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prepared in the 1:1 molar ratio using rotary evaporation method exhibit a higher dissolution profile than the active alone or in a state of physical mixture. Despite their success, the complex preparation by the stated method required an organic solvent which is not desirable. Removal of environmentally harmful organic solvents from the drug product to the levels approved by the Food and Drug Administration is very challenging and therefore conventional techniques used for the preparation of inclusion complexes (co-evaporation, spray drying and kneading) involve several drying steps for considerable time, which may also affect the drug stability (Al-Marzouqi et al., 2006). Hence, it is highly recommended to eliminate the use of organic solvents in the preparation of drugs or drug–cyclodextrin complexes.

The aim of the present study was to produce olanzapine-Me-β-CD complexes in the same stoichiometric ratios (1:1 molar) without using organic solvents or auxiliary agents. Therefore, application of supercritical fluid processing was studied as an alternative to conventional methods in the current work.

A supercritical fluid is defined as a substance that exists above its critical pressure and temperature. Supercritical fluids feature densities like liquids and viscosities and diffusivities like gases and hence offer excellent mass transfer and solubilising properties (York, 1999; Kompella and Koushik, 2001; Sunkara and Kompella, 2002; Bandi et al., 2004). Carbon dioxide becomes supercritical above 31.25 °C and 73.8 bar. Supercritical carbon dioxide (SC-CO_2) is environmentally benign and is considered to be green. SC-CO_2 is a non-combustible, non-toxic, recyclable and environment-friendly solvent (Palakodaty and York, 1999; Lang and Wai, 2001; Lee et al., 2008; Deshpande et al., 2011; Girotra et al., 2013; Rudrangi et al., 2015) and has provided an appealing alternative to toxic organic solvents or conventional complexation media. SC-CO_2 has been successfully employed in the preparation of inclusion complexes between various drugs and cyclodextrins in dynamic or static modes (Table 1).

The use of the SC-CO_2 processing has already been investigated in the preparation of drug-Me-β-CD inclusion complexes (Charoenchaitrakool et al., 2002; Banchero et al., 2013; Rudrangi et al., 2015). A significant improvement in the dissolution rate of drug was observed in all cases. It was suggested by Banchero et al. (2013) that the liquefaction of Me-β-CD in SC-CO_2 favours the complexation of drug and cyclodextrin without any addition of water or auxiliary agents as the drug molecules would better reach the cavity of the cyclodextrin in the molten or liquid state.

The effect of supercritical carbon dioxide processing on the preparation of olanzapine-Me-β-CD complexes has not yet been reported. Inclusion complexes were prepared by physical mixing, freeze drying, co-evaporation and SC-CO_2 processing at various working (temperature and pressure) conditions. The prepared complexes were then characterized by solubility studies, differential scanning calorimetry, X-ray powder diffraction, scanning electron microscopy and dissolution studies.

2. Materials and methods

2.1. Materials

Olanzapine (≥99%, molecular weight: 312.44, CAS number: 132539-06-1) was obtained from Dr. Reddy's Laboratories Ltd. (Hyderabad, Telangana, India). Me-β-CD (average molecular weight: 1310, CAS number: 128446-36-6, extent of labeling: 1.6–2.0 mol CH_3 per unit anhydroglucose) was purchased from Sigma–Aldrich (Gillingham, Dorset, UK). Carbon dioxide (99.9%) was obtained from BOC Ltd. (Guildford, Surrey, UK). All chemicals were used as received without further purification.

Table 1
Drug–cyclodextrin complexes prepared by SC-CO_2 processing in static or dynamic modes.

Drug	Cyclodextrin	Mode	Reference
Acetaminophen	β-CD	Not reported	Giordano et al. (1996)
Benzocaine	β-CD	Static	Al-Marzouqi et al. (2007a)
		Static	Al-Marzouqi et al. (2007b)
Budesonide	HP-β-CD[a]	Static	Bandi et al. (2004)
	γ-CD	Static	Toropainen et al. (2006)
Bupivacaine	β-CD	Static	Al-Marzouqi et al. (2007b)
Econazole	β-CD	Static	Al-Marzouqi et al. (2007c)
		Static	Al-Marzouqi et al. (2009)
Eflucimibe	γ-CD	Not reported	Papet et al. (2003)
	γ-CD	Static	Rodier et al. (2005)
Fluconazole	β-CD	Static	Al-Marzouqi et al. (2009)
Flurbiprofen	TMe-β-CD[b]	Not reported	Moribe et al. (2007)
Ibuprofen	Me-β-CD	Static	Charoenchaitrakool et al. (2002)
	β-CD	Static	Türk et al. (2007)
		Static	Hussein et al. (2007)
Imazalil	β-CD	Static	Lai et al. (2003)
Indomethacin	HP-β-CD	Static	Bandi et al. (2004)
	Me-β-CD	Static	Rudrangi et al. (2015)
Itraconazole	β-CD	Static	Al-Marzouqi et al. (2006)
		Static	Al-Marzouqi et al. (2009)
		Static	Hassan et al. (2007)
Ketoprofen	Me-β-CD	Static	Banchero et al. (2013)
Mepivacaine	β-CD	Static	Al-Marzouqi et al. (2007b)
Miconazole	β-CD	Static	Van Hees et al. (2002)
	HP-γ-CD[c]	Static	Barillaro et al. (2004)
Naproxen	TMe-β-CD	Not reported	Moribe et al. (2007)
	β-CD	Dynamic	Junco et al. (2002)
Piroxicam	β-CD	Static	Van Hees et al. (1999)
		Static	Van Hees et al. (2002)
		Static	Grandelli et al. (2012)
Simvastatin	HP-β-CD	Dynamic	Jun et al. (2007)

In static mode, the contents of the cell are exposed to carbon dioxide, pressurized and allowed to equilibrate; while carbon dioxide is circulated continuously through the cell in the dynamic mode.
[a] HP-β-CD: hydroxypropyl-β-cyclodextrin.
[b] TMe-β-CD: trimethyl-β-cyclodextrin.
[c] HP-γ-CD: hydroxypropyl-γ-cyclodextrin.

2.2. Preparation of binary mixtures of olanzapine with Me-β-CD

All binary mixtures of olanzapine with Me-β-CD were prepared in a 1:1 molar ratio. The processed samples were stored in a desiccator over solid calcium chloride until submitted for analysis.

2.2.1. Physical mixing

Physical mixture was obtained by tumble-mixing an accurately weighed equimolar mixture of olanzapine and Me-β-CD at 100 rpm for 15 min using a TURBULA® T2F mixer (Willy A. Bachofen AG—Maschinenfabrik, Muttenz, Switzerland).