Journal of Molecular Liquids 215 (2016) 135–143

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

Novel pimozide–β-cyclodextrin–polyvinylpyrrolidone inclusion complexes for Tourette syndrome treatment

Hriday Bera [a,b,*], Swathi Chekuri [b], Srimanta Sarkar [c], Sanoj Kumar [b], Nagendra Babu Muvva [b], Srilatha Mothe [b], Jhansirani Nadimpalli [b]

[a] Faculty of Pharmacy, AIMST University, Semeling, Kedah 08100, Malaysia
[b] Gokaraju Rangaraju College of Pharmacy, Bachupally, Hyderabad 500090, India
[c] Department of Pharmacy, Faculty of Science, National University of Singapore, 18 Science Drive 4, Singapore 117543

ARTICLE INFO

Article history:
Received 13 August 2015
Received in revised form 30 November 2015
Accepted 15 December 2015
Available online xxxx

Keywords:
Pimozide
Inclusion complex
Solubility enhancement

ABSTRACT

Pimozide (PMZ), a first-line antipsychotic drug for the treatment of Tourette syndrome, suffers from reduced oral bioavailability problems due to its poor solubility. This study aimed at achieving higher solubility and consequently greater dissolution profile of the drug. Novel PMZ–β-cyclodextrin (β-CD) inclusion complexes in absence and presence of polyvinylpyrrolidone (PVP-K30) were accomplished by kneading method. PMZ formed 1:1 M stoichiometric binary and ternary inclusion complexes as indicated by the A_L-type of phase solubility curves. An improvement in stability constant value (K_S) of PMZ–β-CD complex in the presence of PVP-K30 conferred greater complexation efficiency. The results of FTIR and DSC studies revealed that the indoline ring of PMZ might be accommodated by the β-CD cavity upon complexation. PVP-K30 could establish superior electrostatic interactions and hydrogen bonding contacts in the molecular assembly of the ternary complexes. The incorporation of PVP-K30 also resulted in complete amorphization of the drug in complexes as referred by XRD and SEM studies. As a result, a greater solubility and significantly improved dissolution profiles were achieved when polymer and β-CD were present together in the system. Moreover, immediate release tablets containing ternary complexes [PMZ:β-CD (1:2 M) with PVP-K30 (20%)] exhibited comparable physical properties and improved *in vitro* release profile relative to matrices incorporating pure PMZ. Thus, the ternary inclusion complexes and their formulations could represent a promising therapeutic strategy for Tourette syndrome treatment.

1. Introduction

Tourette syndrome, also known as Gilles de la Tourette syndrome or Tourette's disorder, is a childhood onset neuropsychiatric disorder with a prevalence estimated at 1% of the total global population [1]. The hallmark characteristics are multiple motor and one or more vocal/phonic tics, which could cause substantial physical and psychosocial impairment. In severe cases, it could result in permanent disability [2]. The aetiology and pathophysiology of this complex disorder are not yet well understood. However, the dysfunction of basal ganglia-related circuits and dopaminergic system has been reported to associate with Tourette syndrome [3]. Various neuroleptic drugs with selective D-2 receptor blocking properties have been prescribed traditionally to treat tics caused by Tourette syndrome [2]. Pimozide (PMZ) (Fig. 1A) is an antipsychotic drug of diphenylbutylpiperidine class and is clinically often recommended for the treatment of motor and phonic tics in patients with Tourette syndrome. It works primarily by blocking dopaminergic receptors on neurons in the central nervous system [4]. It belongs to the BCS class II and exhibits poor aqueous solubility. The poor inherent drug solubility and slow dissolution rate in the gastrointestinal tract give rise to difficulties in fabricating suitable pharmaceutical formulations. Moreover, it may also lead to variable oral bioavailability and irreproducible clinical response of the drug [5].

Over the last few decades, emerging data provided convincing evidence that the bioavailability of BCS class II drugs could be improved by enhancing their solubility profiles and dissolution characteristics [6]. A flurry of scientific investigations has employed various approaches like particle size reduction [7], drug dispersion in carrier [8], modification of crystal habit [9], use of surfactants [10], self-emulsifying formulations [5], formation of water-soluble inclusion complexes [11] *etc.* to improve the dissolution profile of the poorly soluble drugs. Among them, the complexation with cyclodextrins (CDs) represents itself as one of the frontier techniques [12]. CDs are structurally interrelated oligosaccharides with six (α-CD), seven (β-CD) and eight (γ-CD) α-1,4-glucopyranose units. They have a lipophilic core with hydrophilic outer surface and exhibit the ability to form noncovalent inclusion complexes with hydrophobic drugs by taking up an entire moiety or some part of it into the cavity [11]. These inclusion complexes have been revealed to enhance the apparent stability, solubility, dissolution rate,

* Corresponding author.
E-mail address: hriday.bera1@gmail.com (H. Bera).

http://dx.doi.org/10.1016/j.molliq.2015.12.054
0167-7322/

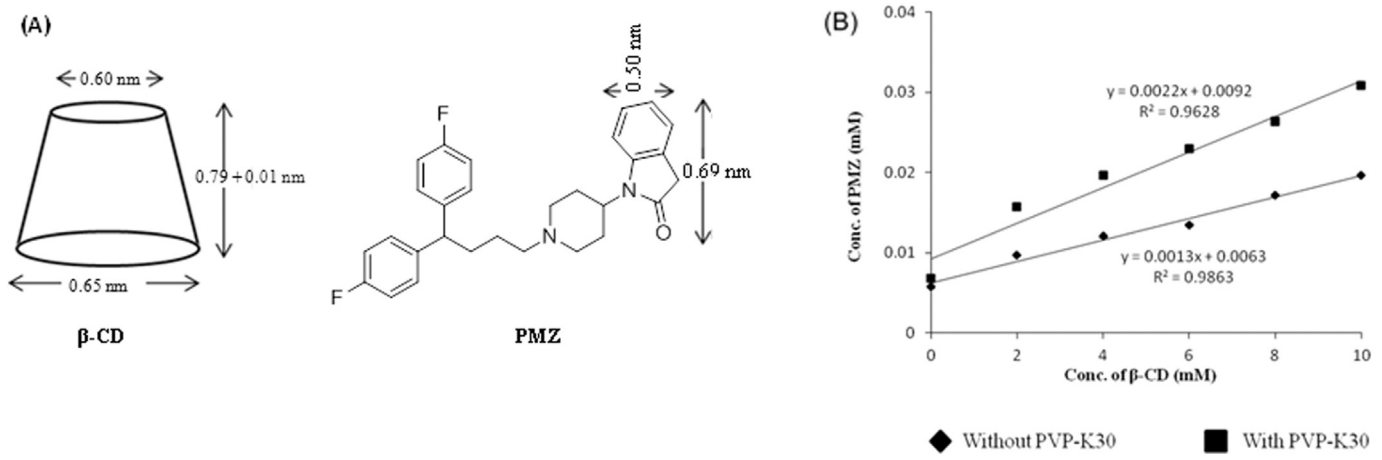

Fig. 1. Molecular sizes of β-CD [35] and PMZ (A) and phase solubility diagram PMZ–β-CD system in presence and absence of PVP-K30 in water at 25 ± 2 °C (B).

and bioavailability of the guest bioactive molecules. Among various cyclodextrins, β-CD is the most frequently used pharmaceutical excipient due to its wide availability, low cost, excellent biocompatibility, wide regulatory acceptance and preferred cavity dimension [13–15]. It is notable that other naturally occurring cyclodextrins (α- and γ-CD) are expensive relative to β-CD. Moreover, recent report provided evidence that β-CD derivative like HP-β-CD is more toxicologically benign than the natural β-CD [16,17]. However, the low aqueous solubility of β-CD is a serious obstruction to its wider application [18].

Pioneering studies in this field demonstrated that the addition of small quantities of a suitable hydrophilic polymer to a drug–β-CD system could augment both the complexation and solubilizing efficiencies of the β-CD and, eventually, it is less demanding on the formulation bulk [16]. Such results are attributed to the synergistic effect of polymer and β-CD on the formation of ternary complexes or co-complexes. The water-soluble polymers could also increase the apparent stability constant of the inclusion complexes [19]. The hydrophilic polymers, due to their direct participation in drug complexation, could alleviate both the pharmaceutical and biological properties of drug–β-CD complexes, irrespective of drug's physiochemical properties [16].

The present work depicts an experimental demonstration of the credibility of novel inclusion complexes of the PMZ with β-CD in absence and presence of polyvinylpyrrolidone (PVP-K30) to improve the solubility and dissolution characteristic of the PMZ. The formation of complexes between PMZ and β-CD and the effect of hydrophilic polymer (PVP-30) on complexation and solubilizing efficiency of β-CD were investigated by phase solubility studies. The PMZ and its inclusion complexes were also characterized by infrared spectroscopy (IR), differential scanning calorimetry (DSC), X-ray diffraction (XRD), and scanning electron microscopy (SEM) analyses. Finally, immediate release tablets were prepared employing inclusion complex with greater dissolution profile and the drug content, various physical properties and *in vitro* dissolution profile of the tablets were compared with the formulation containing pure PMZ.

2. Materials and methods

2.1. Materials

PMZ was received as gift sample from Vasudha Pharma Chem. Ltd. (India). β-CD and PVP-K30 were procured commercially from HiMedia Lab. (India) and FMC Bio Polymer (Ireland), respectively. All the other chemicals and solvents used were of analytical grade and procured commercially.

2.2. Phase solubility studies

Phase solubility studies were carried out in distilled water according to the method described by Higuchi and Connors [20]. An excess amount of PMZ was introduced to 20 ml of aqueous solutions containing various concentrations of β-CD (0–10 mM) with or without fixed concentration of PVP-K30 (0.2% *w*/*v*). The resulting suspensions were shaken on orbital shaking incubator (Kemi, India) at 25 ± 2 °C for 48 h. The drug concentration in the filtered supernatant was assayed spectrophotometrically (Shimadzu/UV-1700, Japan) at 279 nm following suitable dilution. The apparent 1:1 stability constant (K_S) was calculated from the slopes of the phase solubility plots according to the following equation

$$K_s = \frac{\text{Slope}}{S_0(1-\text{Slope})}$$

where S_0 refers the solubility of the drug in absence of β-CD. The complexation efficiency (CE) and the drug:cyclodextrin ratio (D:CD) were also determined using following relationships [21]

$$CE = S_0\, K_{1:1} = [D/CD]/[CD] = \frac{\text{Slope}}{(1-\text{Slope})}$$
$$D/CD = 1/(1 + 1/CE)$$

where [D/CD] denotes the concentration of dissolved complex and [CD] indicates the concentration of dissolved free β-CD.

Gibbs free energy of transfer (ΔG_{tr}°) of PMZ from pure water to aqueous solution of β-CD was estimated according to the equation [22],

$$\Delta G_{tr}^{\mathring{A}} = -2.303RT \log(S_o/S_s)$$

where S_o/S_s is the ratio of the molar solubility of PMZ in aqueous solution of β-CD to that of the pure water.

2.3. Preparation of inclusion complexes

PMZ–β-CD inclusion complexes were prepared in 1:1 and 1:2 M ratios by kneading method with and without addition of PVP-K30. PVP-K30 was added at the concentrations of 0%, 10% and 20% *w*/*w* of the solid complex [19]. The mixture of PMZ, β-CD and PVP-K30 in required quantities was triturated in a mortar with a small volume of water:methanol (1:1 *v*/*v*) solution until a homogenous paste was formed. The paste was kneaded for 45 min and then dried at 45 °C for 24 h in an oven. The dried mass was pulverized and sieved through