DISSOLUTION RATE ENHANCEMENT AND PHYSICOCHEMICAL CHARACTERIZATION OF NAFTOPIDIL IN SOLID DISPERSIONS WITH B-CD AND HP B-CD

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ARTICLE INFO

Article history
Received 31/12/2014
Available online
1503/2015

Keywords
Naftopidil,
Solid Dispersion,
Kneading Method,
Beta Cyclodextrin,
Hydroxy Propyl
Beta Cyclodextrin.

ABSTRACT

Naftopidil, (R,S)-1-[(2-methoxyphenyl)-l-piperazinyl]-3-(l-naphthyloxy)2-propanol, is a novel antihypertensive agent. Naftopidil is practically insoluble in water. The present study was carried out to enhance dissolution properties of naftopidil through the preparation of solid dispersions using β-cyclodextrine (β-CD) and hydroxy propyl β-cyclodextrine (HP β-CD) as carrier at various proportions by using kneading method and by the physical mixture method. Solid dispersions of Naftopidil with carriers were prepared in different drug: carrier ratios such as (1:1, 1:3, 1:5) using techniques like physical mixing (PM) and kneading method (KM). The drug release profile was studied in pH 1.2 HCl solution. The DSC and FTIR analysis was carried out to study the compatibility between drug and carrier. UV spectrophotometric method was selected for assay as well as in-vitro dissolution studies at 280nm. The solid dispersion using HP β-CD and napthopidil exhibited superior dissolution profile than pure drug.

Please cite this article in press as Rahul Patil et al. Dissolution rate enhancement and physicochemical characterization of naftopidil in solid dispersions with β-CD and HP β-CD. Indo American Journal of Pharm Research,2015:5(02).

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INTRODUCTION

Naftopidil, (R, S)-1-[(2-methoxyphenyl)-1-piperazinyl]-3-(1-naphthoxy)-2-propanol α1-adrenergic receptor antagonist has been indicated for the treatment of benign prostatic hyperplasia. Naftopidil is practically insoluble in water [1, 2]. The rate of dissolution can be increased by increasing the surface area of available drug by various methods like micronization, complexation and solid dispersion (SD) [3]. Hence, an attempt was made to improve the dissolution characteristics using the solid dispersion technologies. Among various approaches to improve the dissolution rate of poorly soluble drugs, the preparation of solid dispersions has often proved to be successful [4, 5, 6, 7], nifedipine [8], meloxicam [9], lansoprazole [10], valdecoxib [11], aceclofenac, carbamazepine, glimipiride. Various hydrophilic carries, such as poly ethylene glycols [12], cyclodextrins, polyvinyl pyrrolidone [13], sugars [14], urea [15] have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs. In the present work, solid dispersions of Naftopidil with β-Cyclodextrins (β-CD), hydroxypropyl β-Cyclodextrins (HP β-CD) were prepared in different drug: carrier ratios (1:1, 1:3, 1:5) using techniques like physical mixing (PM) and kneading method (KM), to improve solubility and dissolution characteristics. UV Spectrophotometric method was selected for assay as well as in-vitro dissolution studies at 280 nm in pH 1.2 HCl solution. The increased in dissolution rate of the drug may be due to increased wettability, hydrophilic nature of the carrier and also possibility due to reduction in drug crystallinity.

MATERIALS AND METHODS

Materials

Naftopidil was a gift sample from Cadila Healthcare Pvt. Ltd (Baroda, India), β-Cyclodextrins and Hydroxypropyl β-Cyclodextrins were purchased from Sigma Aldrich GmbH (St. Lous, USA). All other reagents and solvents were of analytical grade and used without further purification.

Methods

Preparation of solid dispersions:

Physical mixture and solid dispersion with cyclodextrins and naphtopidil were prepared as per following procedure.

1. Physical mixtures: The physical mixtures (PM) were prepared by geometric mixing of drug and β-CD or HP β-CD in a mortar and pestle with simple trituration for 15–20 min and then passing the mixture through a 60# sieve.

2. Solid dispersion (SD): Inclusion complexes of naftopidil with β-CD and HP β-CD in the weight ratios of 1:1, 1:3, and 1:5 were prepared by a kneading technique. Solid dispersions were prepared by mixing drug with β-CD or HP β-CD and then kneading the same with a mixture of ethanol–water (1:9) to obtain a mass with a pasty consistency. This was then dried in a hot air oven at 45–50 °C. All the dispersions were prepared in triplicate, sieved through British Standard Sieve (BSS) 60# (180-μm diameter), and stored over anhydrous calcium chloride in a desiccator.

Solubility Measurements and Phase Solubility Study:

Solubility measurements were performed according to the method of Higuchi and Connors [16]. Various aqueous solutions (3, 6, 9, 12 and 15 mM) of β-CD and HP β-CD were prepared, and 10 mL of each solution was taken into separate glass vials. An excess amount of drug was added to these vials. The vials containing drug–hydrophilic polymer carrier mixtures were shaken at 37 ± 0.1 °C for 48 h in a water bath shaker (Remi Pvt Ltd, Mumbai). After 48 hrs, samples were filtered through 0.45-μm filter paper. The filtrate was suitably diluted with corresponding polymer carrier solution (3, 6, 9, 12 and 15 mM) and analyzed spectrophotometrically at 280.0 nm using a UV spectrophotometer (Shimadzu UV-1700, Pharm Spec) [17]. Solubility studies were performed in triplicate (n = 3) [18].

In Vitro Dissolution Studies:

Dissolution studies of naftopidil in powder form, SDs, and PMs were performed using a digital USP dissolution Apparatus 2 (Electrolab TDT-08L) at a paddle rotation speed of 50 rpm in pH 1.2 HCl solution as dissolution medium at 37 ±0.5 °C. SDs or PMs equivalent to 75.00 mg of naftopidil was weighed using a digital balance (AUX 120 Shimadzu) and added to the dissolution medium. At specified times (5, 10, 15, 30, 45, 60 min.), 5-mL samples were withdrawn using a 0.45-μm syringe filter (Seyprane, Mumbai) and then assayed for the naftopidil content by measuring the absorbance at 280.0 nm using a UV-vis spectrophotometer (Shimadzu UV-1700, Pharm Spec). Fresh medium (5 mL) that was maintained at 37 °C was added to the dissolution medium after each sampling to maintain a constant volume throughout the test. Dissolution studies were performed in triplicate (n = 3), and calculated mean values of cumulative drug release were used to plot the release curves (12).

Fourier Transform Infrared spectroscopy:

Infrared spectra were obtained using an FTIR spectrometer (Model 430, Shimadzu, Japan). The samples (naftopidil or SDs) were ground and mixed thoroughly with potassium bromide, an infrared-transparent matrix, at 1:100 (sample/KBr). The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Scans were obtained from 4000 to 400 cm-1 at a resolution of 2 cm-1.
Differential Scanning Calorimetry:

The DSC analysis was carried out to detect any interaction between drug and carrier. The DSC measurements were performed on a DSC–1 Star® System (Mettler Toledo) differential scanning calorimeter with a thermal analyzer. All accurately weighed samples (about 2 mg of naftopidil or its equivalent) were placed in sealed aluminum pans before heating under nitrogen flow (20 mL/min) at a scanning rate of 10 °C min–1 from 50 to 400°C.

RESULTS

Solubility Studies:

Phase solubility diagrams showed a linear increase in drug solubility with an increase in the concentration of each examined carrier (Figure no. 1, 2). At 15 mM concentration of β-CD, HP β-CD, the solubility of naftopidil increased significantly. Analogous results were found for these same carriers, probably due to the formation of weakly soluble complexes. Hydrophilic carriers mainly interact with drug molecules by electrostatic bonds (ion-to-ion, ion-to-dipole, and dipole-to-dipole bonds), even though other types of forces, such as van der Waals forces and hydrogen bonds, can frequently play a role in the drug–carrier interaction (19). The drug solubility increased linearly with increasing polymer concentration (18).

In Vitro Dissolution Studies:

All formulations of naftopidil were subjected to in vitro dissolution studies using 0.1N HCl solution at pH 1.2 as the dissolution medium to assess various dissolution properties. All SD formulations with various polymers exhibited higher rates of dissolution than naftopidil pure drug and corresponding physical mixtures. The pure drug showed up to 60% dissolution over 60 min, but solid dispersions of β-CD and HP β-CD prepared by kneading and physical mixture showed higher dissolution profiles (Figure no. 3). Compared with physical mixture method, kneading method for solid dispersions showed better results of about 82% within 10 min of dissolution study, but only about 50% for physical mixture method. The dissolution enhancing effect of various carriers used in this study followed the order: HP β-CD > β-CD. The dissolution rate of naftopidil from physical mixtures (1:5) with both carriers was up to 65% higher than that of pure naftopidil (40%) within 45 min (Figure no. 4). In this case (physical mixture), the increased dissolution rate observed can be attributed to several factors such as a solubilization effect of these carriers, improved wettability of the drug, and inhibition of particle aggregation. The results of dissolution studies for the different formulations in terms of percent dissolved at 10 min (Q10), 30 min (Q30), 45 min (Q45) and 60 min (Q60) are shown in (Table 1).

![Figure no. 01: Phase solubility diagram of naftopidil using β CD.](image1)

![Figure no. 02: Phase solubility diagram of naftopidil using HP β- CD.](image2)

![Figure no. 03: Phase solubility diagram of naftopidil using β CD.](image3)

![Figure no. 04: Phase solubility diagram of naftopidil using HP β- CD.](image4)
Table no.1: Percent Drug Dissolved within 60 min for pure naftopidil and naftopidil with β-CD and HP β-CD Binary Systems (n=3).

<table>
<thead>
<tr>
<th>Sample</th>
<th>Drug/ Polymer Ratio</th>
<th>Naftopidil Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$Q_{10}$</td>
</tr>
<tr>
<td>Naftopidil</td>
<td>-------</td>
<td>40.1</td>
</tr>
<tr>
<td>Naftopidil:β CD (Physical Mixture)</td>
<td>1:1</td>
<td>30.58</td>
</tr>
<tr>
<td></td>
<td>1:3</td>
<td>46.19</td>
</tr>
<tr>
<td></td>
<td>1:5</td>
<td>42.79</td>
</tr>
<tr>
<td></td>
<td>1:1</td>
<td>85.73</td>
</tr>
<tr>
<td>Naftopidil:β CD (Kneading method)</td>
<td>1:3</td>
<td>78.75</td>
</tr>
<tr>
<td></td>
<td>1:5</td>
<td>67.92</td>
</tr>
<tr>
<td></td>
<td>1:1</td>
<td>43.82</td>
</tr>
<tr>
<td>Naftopidil: HP β CD (Physical Mixture)</td>
<td>1:3</td>
<td>49.34</td>
</tr>
<tr>
<td></td>
<td>1:5</td>
<td>52.39</td>
</tr>
<tr>
<td></td>
<td>1:1</td>
<td>88.25</td>
</tr>
<tr>
<td>Naftopidil: HP β CD (Kneading method)</td>
<td>1:3</td>
<td>90.75</td>
</tr>
<tr>
<td></td>
<td>1:5</td>
<td>82.52</td>
</tr>
</tbody>
</table>

Figure no. 03. In vitro dissolution profiles of pure naftopidil, naftopidil Solid Dispersion and Physical Mixtures with β-CD.

Figure no. 04. In vitro dissolution profiles of pure Naftopidil, naftopidil Solid Dispersion and Physical Mixtures with HP β-CD.
Fourier Transform Infrared spectroscopy:

The interaction between the drug and carrier often leads to identifiable changes in the IR profile of SDs. The IR spectra of SDs were compared with the standard spectrum of naftopidil (Figure no. 4, 5). In the IR spectrum of naftopidil, the band at 2934 cm$^{-1}$ and 3063 cm$^{-1}$ indicates a aromatic C–H group stretching vibration. Bands in the range of 1303–996 cm$^{-1}$ confirm the presence of a C–O bond. The presence of a band at 1593 cm$^{-1}$ and 1499 cm$^{-1}$ indicates benzene. The peak at 2881 cm$^{-1}$ is due to CH$_3$ symmetric stretching. The peak at 1050 cm$^{-1}$ indicates the presence of a C–N bond. The complex region of 900–600 cm$^{-1}$ indicates skeletal vibration and an aromatic ring in the drug substance. The IR spectrum for drug–β-CD SDs reveals a peak at 2933 cm$^{-1}$ and 3049 cm$^{-1}$ due to aromatic C–H group stretching. A peak in the range of 1267–997 cm$^{-1}$ indicates C–O bond. A significant peak at 2933 cm$^{-1}$ and 3048 cm$^{-1}$ in the IR spectrum of drug–HP β–CD SDs is due to aromatic C–H group stretching vibration. The characteristic peaks for C–O is located in the same range for the SDs as for the pure drug. The spectrum reveals the characteristic peaks in the typical range (C–O at 1300–1000 cm$^{-1}$, C–H stretching at 2933 cm$^{-1}$, and an aromatic ring at 900–600 cm$^{-1}$) inferring no significant interaction between drug and carrier in the solid dispersions.

Differential Scanning Calorimetry:

Differential scanning calorimetry enables the quantitative detection of all processes in which energy is required or produced (i.e., endothermic and exothermic phase transformations). The DSC thermograms for pure drug and SDs are shown in Figure 5. The DSC thermogram of Naftopidil shows an intense endothermic peak at 127.96 °C corresponding to its melting point. The onset of melting was observed at 126.26 °C. The DSC thermogram of naftopidil with β-CD showed a peak at 124.84 °C for the drug and also at 104.59 °C indicating drug amorphization. With HP β-CD peak for drug observed at 127.02 °C and for HP β-CD peak observed at 260.61 °C indicating that no significant interaction between naftopidil and the hydrophilic carriers (Figure no. 6) [20].

Figure no. 05: Fourier Transform Infrared spectrum of A) Naftopidil B) Naftopidil –β-CD and C) Naftopidil HP–β-CD.

Figure no. 06: Overlay DSC thermogram of Naftopidil, Naftopidil –β-CD and Naftopidil HP–β-CD.
DISCUSSION

The phase solubility study with water and various hydrophilic carriers showed an increase in the solubility of the drug in the presence of the carriers. All SD formulations with various polymers exhibited higher rate of dissolution values than naftopidil pure drug and corresponding physical mixtures.

The pure drug showed up to 50% dissolution over 60 min, but its solid dispersions prepared by kneading method with (1:3 and 1:5 w/w) showed dissolution of more than 80% over 10 min. The dissolution enhancing effect of various carriers used in this study followed the order: HP β-CD > β-CD. This enhancement of naftopidil dissolution from drug carrier systems can be ascribed to several factors. Lack of crystallinity (i.e., amorphization), increased wettability and dispersibility, and particle size reduction are considered important factors for dissolution rate enhancement [21].

FTIR spectroscopy showed that individual peak characteristics are retained in the spectra of drug and hydrophilic carriers, indicating there is no interaction between the drug and the carriers. The DSC study reveals no significant interaction between naftopidil and the hydrophilic carriers used; there is change in the crystallinity of pure naftopidil to amorphous state in the solid dispersions.

A similar result of improvement in the solubility of glipizide by the hydrophilic polymer’s solid dispersion is reported by P. Ramasubramaniyan et al. [22].

CONCLUSION

The solubility and dissolution rate of naftopidil can be enhanced by the use of naftopidil SDs with β-CD and HP β-CD. Compared with β-CD, HP β-CD showed better enhancement of dissolution. From FTIR spectroscopy it was concluded that there were no well-defined chemical interactions between naftopidil and β-CD, or HP β-CD in the solid dispersions. The DSC study also confirmed the same result; however, there is a change in crystallinity of pure Naftopidil to amorphous state in the solid dispersions. The solid dispersions conclusively indicated that this is a very fruitful approach to improve the dissolution rate and oral bioavailability of poorly soluble drug naftopidil.

REFERENCES


