Open Access Journal

Indian Journal of Medical Research and Pharmaceutical Sciences

November 2018;5(11) ISSN: ISSN: 2349-5340

DOI: 10.5281/zenodo.1490679 Impact Factor: 4.054

PHASE SOLUBILITY ASSESSMENT OF POSACONAZOLE

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Keywords:

Posaconaole; β-Cyclodextrin; HPMC; Carbopol; Mucoadhesive.

Abstract

An attempt was made to design and develop mucoadhesive tablet formulation of posaconazole against candida albicans in immunocompromised pateints. Poorly soluble drugs are very challenging to formlate in oral mucoadhesive dosage form. Whereas lipophilic drugs, well absorbed through oral mucosa, but shows very low fluxes hence exhibit difficulty in transport across mucosa. The complexation of posaconazole with β- cyclodextrin was studied by phase solubility method which indicates the formation of complex with 1:1 stoichiometry. The muccoadhesive tablets for the delivery of posaconazole were prepared by compression using carbopol and HPMC. The assessment of buccal administration of posaconazole was analyzed by penetration through in-vitro excised goat mucosa. The results of experimented study reveals that, as there was increase in drug release rate from the tablets in solution as well as an increase in the amount of posaconazole permeated through sheep buccal mucosa. An attempt was made to study the suitability of posacanazole in buccal drug delivery system.

Introduction

Oral mucosa is richly supplied with blood vessels which prove to be ideal site of administration to treat oral candidiasis locally. Moreover this route provides additional advantage over oral route to overcome the demerits of drug inactivation by first pass effect and gastrointestinal. The buccal route of administration improves the bioavailability of drug and its action locally. Oral caniddiasis of very common infection that occurs commonly in immunocompromised pateints. The use of water soluble adhesive polymers to designed mucoadhesive tablet is to retain the dosage form on site of adhesion for the proposed time. Certain merits like self-medication, non-painful, improved bioavailability and decreased first pass effect proves mucoadhesive tablet as an ideal route of administration. Muccoadhesive tablet provides increase retention time of tablet on site of adhesion there by releasing the drug at a constant rate locally. Posaconazole is newer broad spectrum traiazole poorly soluble drug to treat severe fungal infections.Due to lower bioavailability when taken orally posaconazole is choosen as an ideal candidate to formulate as mucoadheive tablet using water soluble adhesive polymers. Hence in the proposed work to formulate and develop mucoadhesive tablet of posaconazole by complexation with β- Cyclodextrin for the treatment of oral candidiasis.

Materials and method

Posaconazole was generously gifted by Ajanta Pharmaceuticals Ltd., Mumbai. β- Cyclodextrin was gifted by strides arco lab, Bangalore. Hydroxypropyl methylcellulose K4M was obtained as a gift sample from Colorcon Asia Limited, Goa. Carbopol 934P was provided by Central Drug House India, ethyl cellulose (10cps), lactose DC was purchased from SD Fine Chem. Mumbai, India.

Method:

1. Solubility Assesment Studies of Posaconazolewith β-Cyclodextrins

Phase solubility assesment is used to determine stoichiometric proportion of the posaconazole and β-Cyclodextrinsto derive the stability constant of resulting complexes. From this study it is determine that how the complexes of β-cyclodextrin affect the solubility of the Posaconazole. Excess amounts of Posaconazole were added to 10 ml of phosphate buffer solutions (pH 7.4) containing various concentrations of β-cyclodextrin. The solutions formed were sonicated for 15 min and were shaken for 3 days in a water bath at 40 ^{0}C. After specified period of time, the solution is filtered. The filtered solutions were appropriately diluted and the amount of dissolved Posaconazole was

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determined using a UV-visble spectrophotometer at 262 nm. Previous determinations showed that β-CD did not interfere with the spectrophotometric measurements.The stability constant of Posaconazoleβ-cycldextrincomplex was calculated using Higuchi and Connor's equation.

$$K_{(1:1)} = \frac{\text{Slope}}{S_0 (1 - \text{slope})}$$

Where,

S_0 = Intrinsic solubility of Posaconazole in aqueous complexation media (phosphate buffer) "slope" was calculated from phase solubility diagram.

Table-1: Data for phase solubility analysis studies of Posaconazole complexes with β-Cyclodextrin

Concentration of β-CD x 10^{-3} moles/ liter	Concentrations of Posaconazole x 10^{-3} moles/liter
0	0.169±0.001
1.1	0.721±0.015
2.2	1.32±0.026
3.3	1.806±0.02
4.4	2.50±0.015

*Average of three determination

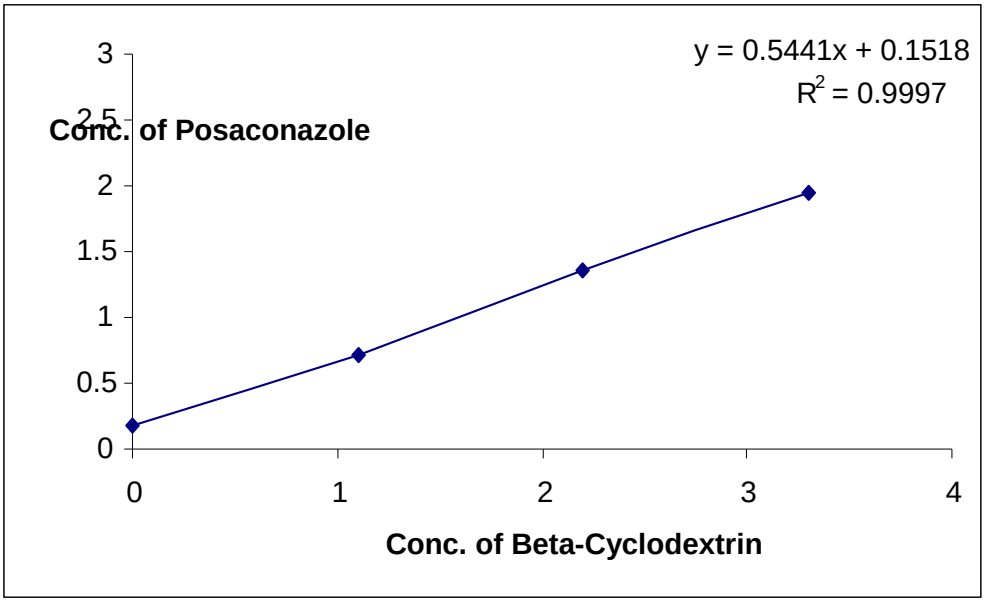

Figure-1: Phase solubility analysis of posaconazole withβ-cyclodextrin

2. Formulation of complexes of Posaconazole with β-cyclodextrin.

Posaconazole and β-CD were dissolved in water and methanol. The two solutions were heated to 65^0C separately and mixed together. The mixture was cooled to 0^0C and allow to crystalized and filtered. The crystals were allowed to dry overnight.

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Assay of complexes:
50 mg of drug complex powders which is equivalent to 20mg of Posaconazole was accurately weighted and transferred to 100ml of volumetric flask volume was made up to the mark with methanol. After appropriate dilutions with methanol drug contents for complex were measured spectrophotometricaly at 262nm.

3. Dissolution profile of Posaconazole and complex:
Quantity of complex sample equivalent to 10 mg of Posaconazole was kept for drying for 24hrs at 40ºC and then was subjected to dissolution test using dissolution test apparatus type II. Pure posaconazole powder (10 mg) was used as control and was also subjected to similar dissolution test. inclusionComplex powder equivalent to 10 mg of posaconazole were placed in dissolution medium and apparatus was run.10ml aliquots were withdrawn at time intervals of 10min, up to 120 min. and each time 10 ml of fresh dissolution medium maintained at same temperature was added.

Table- 2: Dissolution data for Posaconazole and complex.

Time (Min.)	Cumulative Percentage of Drug Released (%)	
	Posaconazole	Posaconazole - β-cyclodextrin complexes
10	20.72 ±0.53	43.50 ± 0.23
20	23.48 ±0.91	52.33±0.11
30	27.30±0.72	59.54±0.68
40	30.12±0.45	66.50 ±0.15
50	35.30 ±0.45	70.42±0.50
60	37.68±0.29	78.64±0.19
70	39.50 ±0.75	84.55±0.75
80	41.23±0.55	89.85± 0.68
90	43.39 ±0.61	92.30±0.15
100	45.58±0.61	95.48±0.75
110	46.78±0.23	99.55±0.19
120	49.80 ±0.17	-
T50 (Min.)	108	18.00
T90 (Min.)	> 120	83.00

* Average of three determination.

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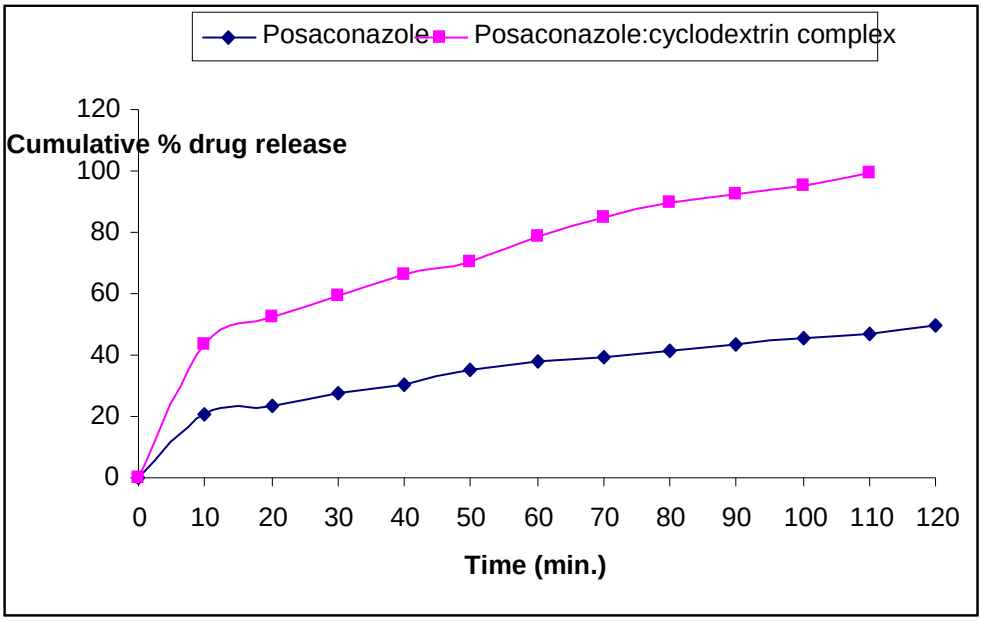

Figure-2: Dissolution profiles of Posaconazole and Posaconazole - β-cyclodextrin

Result and discussion

The aim of the work is to formulate a mucoadhesive tablet of poorly soluble drug posaconazole by improving its solubility with incorporation of β-cyclodextrin and formation of inclusion complex to increase the bioavailability of the drug. Hydroxy propyl mthyl cellulose and carbapole were used as the polymer of choice for mucoadhesion property and ethyl cellulose used as backing polymer for unidirectional release of drug at the site of administration. The inclusion complex of posaconazole and β-cyclodextrin was prepared by co-precipitation method. The dissolution profile of the inclusion complex shows better dissolution profile i.e 100% in 115 minutes. Phase solubility analysis of posaconazole β-cyclodextrin inclusion complex was performed and result shows gradual increase in the solubility of posaconazole as the concentration of β-cyclodextrin increases. By the help of phase solubility data equal molar concentrations of posaconazole β-cyclodextrin inclusion complex was prepared by co-precipitation method.

Conclusion

The antifungal drug posaconazole is an important substitute for the oral candiasis which is refractory to other triazole derivatives. Apart from being ideal candidate for mucoadhesive dosage forms it is poorly water soluble, hence β-cyclodextrin was used as complexing agent to prepare inclusion type of complex to improve the solubility of the posaconazole. The complex does not penetrate the mucosa instead it releases continuously the free drug to maintain its constant release throughout the duration of treatment. The β-cyclodextrinalong with increasing the solubility also performs mucoadhesion.

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