Solubility studies of rifampicin and hydroxypropyl-ß-cyclodextrin for pediatric formulations

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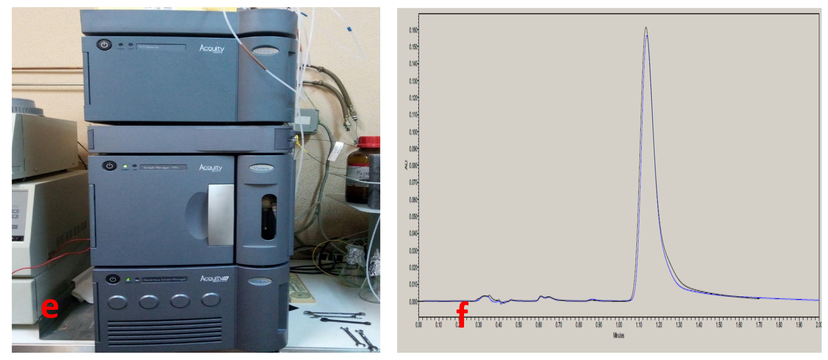
INTRODUCTION AND AIM

In this work the complexation properties of a hydroxypropyl-ß-cyclodextrin (HPBCD) with an antituberculous drug of low solubility and low intestinal permeability classified as BCS Class IV, like as is Rifampicin (R), are studied [1]. Changes of the bioavailability of R in at fixed dose combination (FDC) has been widely recognized in numerous scientific publications [2]. Pediatric formulations have big limitations and are being of special interest those liquid oral pharmaceutical preparations of a single dose. Our aim is to analyze the ability of this cyclodextrin derivative to solubilize oral pediatric doses of Rifampicin

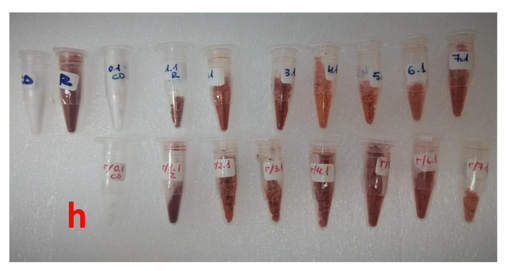
MATERIALS AND METHODS

Rifampicin was provided by Fagron (Barcelona, Spain) and HPBCD, Kleptose HPB® (degree of substitution 0.65) was donated by Roquette Frères (Lestrem, France). All chemical were UPLC and analytical grade (Sigma-Aldrich, Spain). Rifampicin was analyzed by reversed-phase in an Acquity UHPLC® H-Class System (Wates, Milford, MA, USA).

The method was validated for a concentration interval of 10-22.5 μg/mL. The ANOVA of the linear regression confirmed the linearity of the method (α=0.05) and the quantification of R accurately and precisely (data not shown).



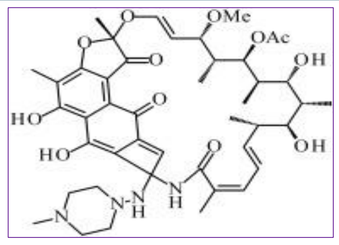
Solubility studies were carried out according to Higuchi and Connors (3). For that, an excess amount of R was added to 5 ml of cyclodextrin solution with different concentrations (0 to 179 mM) in Sorensen phosphate buffer solutions at different pHs (a, b). All samples were prepared in duplicate. The suspensions were stirring at 25ºC in amber glass vials during 3 days (c, d). After equilibrium was reached, the suspensions were filtered using 0.45 μm and 0.22 μm syringe filters, and it analyzed the R concentration of each vial by chromatography method (e, f).



To the characterization of the interaction of R and HPBCD, we have employed the freeze-drying method (g, h). All solid products lyophilized (obtained from the residual and the solution) were characterized by differential scanning calorimetry (DSC) and infrared spectroscopy (IR) techniques.

RESULTS AND DISCUSSION

Figure 1. Rifampicin



PART A: The solubility of the drug increases linearly as a function of the CD concentration, showing a water-soluble complexes (A_L type). Apparent 1:1 stability constants (Kc) of the R-HPBCD complexes were calculated from the slope of the straight portion of the phase solubility diagrams using the equation: Kc = slope/So (1-slope), where So is the solubility of the drug in buffer solution. The solubility of R is greater between 2 to 7 seven times than without CD. The concentration maximum for forming a water-soluble complex of R and HPBCD is lower at higher pH. So that at pH 6.8 the limit concentration is 71 mM and at pH 7.4 is 64 mM (at pH 8.0 is 54 mM data no shown). These results indicate the complexation process of R with HPBCD is strongly influenced by ionization of the drug. (Table 1).

PART B: In function of pH, the CD solubility is depressed by the presence of the drug between a CD concentration of 65 to 100 mM, giving rise inclusion complexes of solubility limited (Bs-Type). The structural characteristics of the complexes in solution and the solid residual lyophilized obtained in at pH 7.4 studies were different. Figure 3 and 4 show the existent of an inclusion complexes R-HPBCD mixture with R and CD not complexed.

Table 1. Apparent stability constant of water –soluble complexes R-HPBCD (1:1)

pH	HPBCD (mM)	Kc (M^{-1})	CE
6,8	0 - 71.0	777,6	0,154
7,4	0 – 64.0	73,8	0,245

PART C: The increase of solubility of the drug linearly again as a function CD above 100 M concentration is due to self-association process CD-CD and drug-drug and theirs interactions.

Figure 2. Phase solubility diagrams for R in the presence of HPBCD at different pHs, 6,8 and 7,4 of phosphate solutions at 25ºC (n=2)

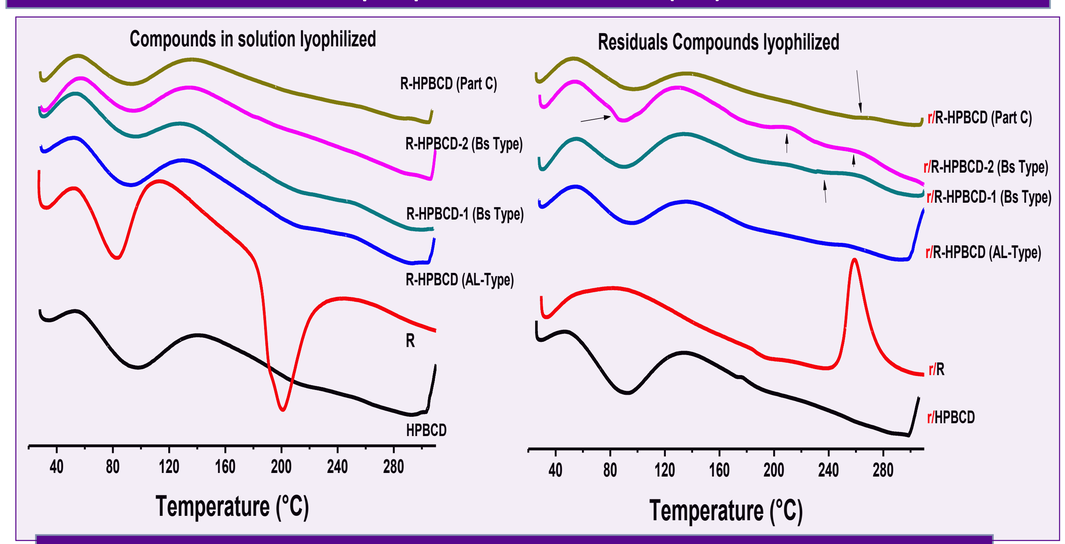


Figure 3. Differential scanning calorimetry results

By DSC ad IR Techniques we observed different thermal behavior and spectral characteristic of R and HPBCD samples lyophilized (see figure 3 y 4). By these techniques can tested the formation of inclusion complexes R-HPBCD and other compounds for self-assembled process that give rise aggregates that decrease or increase the drug solubility [4].

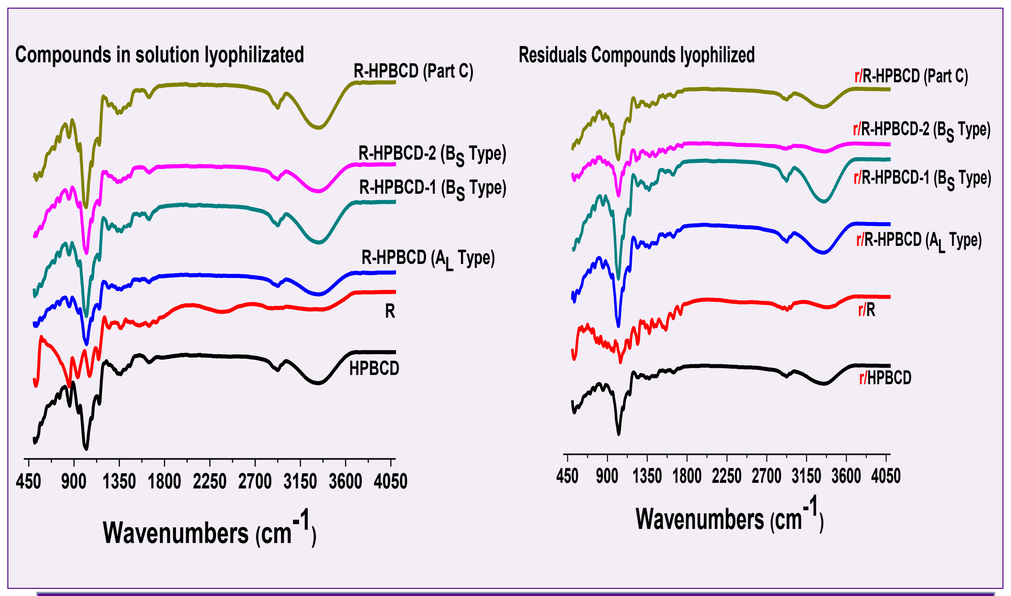


Figure 4. Infrared spectra results

CONCLUSIONS

R form inclusion complexes with HPBCD of different solubilities in phosphate buffer solutions at different pHs. By complexation process, the solubility of R increase between two to seven times. The ionization of this drug defines the interaction with this cyclodextrin derivative and also the final solubility of the drug due to self-association effects drug-drug and cyclodextrin.

REFERENCES

[1] T.T. Mariappan, Saranjit Singh, Clinical Research and Regulatory Affairs, 23 (1), 1-10, 2006.
[2] M . Sosa, M.E. Széliga, A. Fernández, C. Bregni. Ars Pharm. 46(4), 353-364, 2005
[3] T. Loftsson, ME Brewster. Journal of pharmaceutical science, 101, 9, 3019-3032, 2012.
[4] C. Schönbeck, T.L. Maden, G.H. Peters, R. Holm, T. Loftsson. Int. J. Pharm., 531, 504-511, 2017.

ACKNOWLEDGMENTS

The authors wish to thank of ACIISI (ProlD2017010094) for financial support and Roquette Frères for supplying hydroxypropyl-ß-cyclodextrin