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Ethanol Based Formulations and the Solubility- Permeability Interplay; does Ethanol Increase the Intestinal Permeability?

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1. Introduction

according to the BCS, two main factors that control oral drug absorption are the solubility of the drug in the aqueous intestinal milieu, and its permeability throughout the gastrointestinal (GI) membrane[1]. Solubility- enabling formulations allow substantial solubility increase of lipophilic drugs; however, the drug's bioavailability often remains unchanged or even decreases with these formulations. We have previously explained this phenomenon by the solubility-permeability tradeoff; while many solubility-enabling formulations dramatically increase the apparent solubility of the drug, the permeability may be concomitantly decreased[2]. Ethanol is commonly used cosolvent in many pharmaceutical formulations, due to its high ability to increase the solubility of poorly water-soluble drugs[3]. However, its solubility- permeability interplay was not studied yet. On one hand, it was reported that ethanol may increase the mucosal and microvascular permeability of the jejunum, on the other hand, it was reported that ethanol did not increase in vivo plasma exposure of lipophilic drugs[4]. The aim of the current research is to study the solubility, the permeability and the solubility-permeability interplay of the lipophilic drug carbamazepine)CBZ (when it was formulated with increasing levels of ethanol.

2. Materials and methods

The solubility of CBZ was studied in presence of increasing levels of ethanol (0-40%). The drug's intestinal permeability from different ethanol formulations was studied in-vitro, using caco-2 cells and in-vivo, using rat jejunum perfusion method (***Figure 1***). Drug quantification in all samples was analyzed by UPLC. Ethanol levels in the samples were studied by Ethanol Assay Kit. The predicted permeability at a given % ethanol (P_m) was calcu-

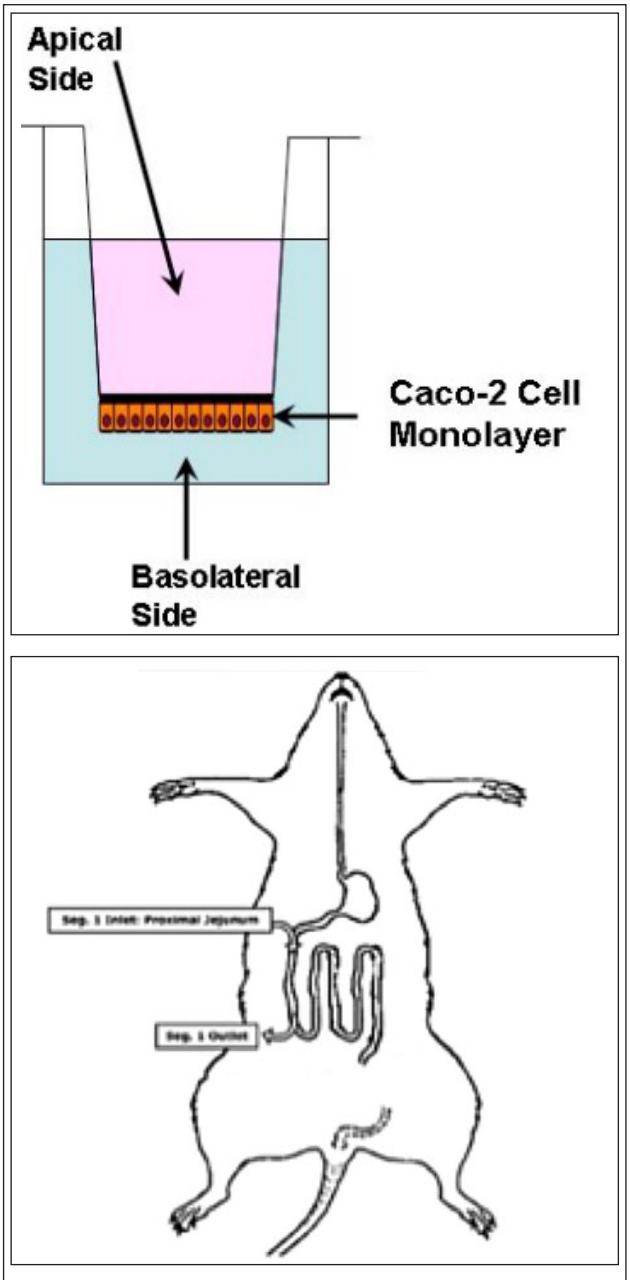

Figure 1 *Illustration of the permeability experiments using caco-2 cells (top panel) and single-pass intestinal perfusion (SPIP) method (bottom panel).*

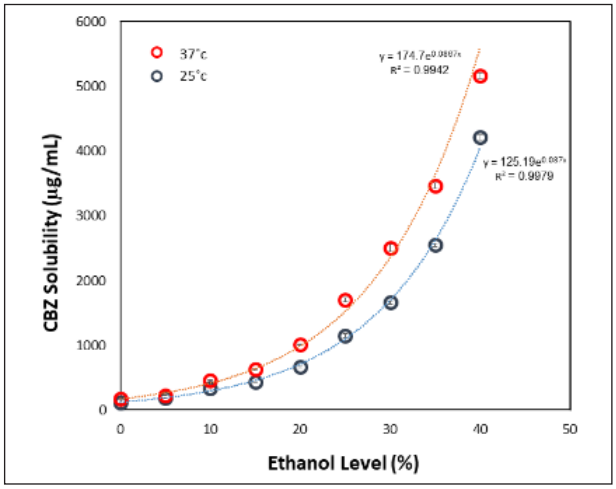

Figure 2: *The solubility of CBZ in ethanol based formulations, at room temperature (25 ˚C) and at 37 ˚C.*

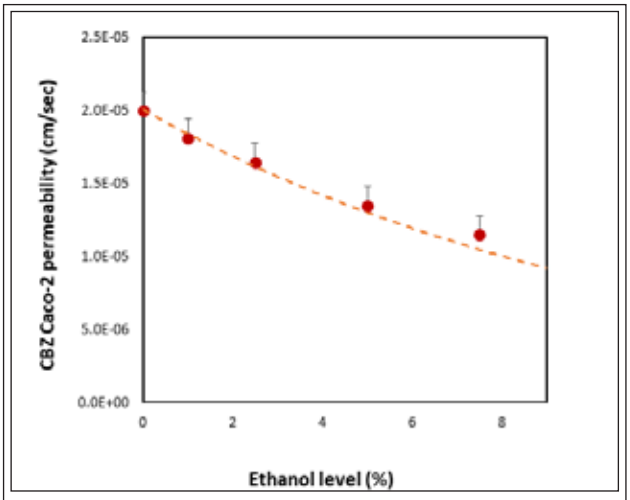

Figure 4: *CBZ experimental vs. theoretical permeability values through caco-2 cells, in presence of increasing ethanol levels.*

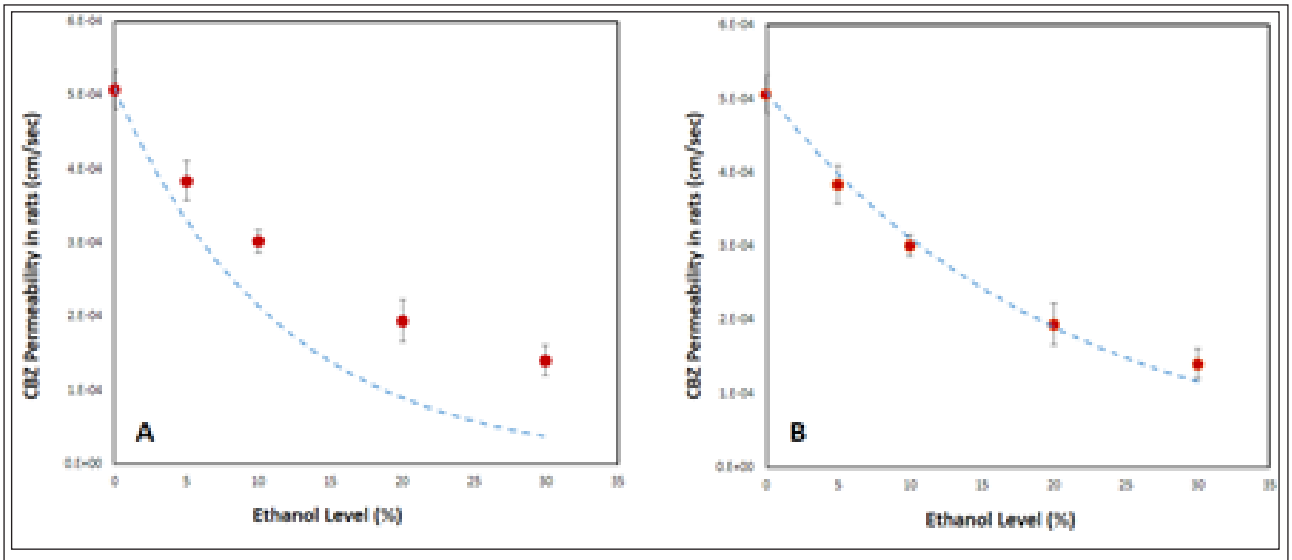

Figure 3: *CBZ experimental vs. theoretical permeability values in presence of increasing ethanol levels. Initial ethanol formulation concentrations (4a), vs. the real ethanol formulation concentrations after absorption (4b)were used for the theoretical calculations.*

lated using the equation: (P_m) is equal to the permeability of CBZ, in the absence of solubilizer ($P_m(0)$) times the aqueous solubility of CBZ in the absence of solubilizer ($S_{aq}(0)$) divided by the apparent solubility of the drug at the relevant % ethanol (S_{aq}). Then the experimental permeability was compared to the calculated theoretical permeability. The resulting solubility-permeability interplay was analyzed.

3. Results

ethanol significantly enhanced the solubility of CBZ, in concentration dependent manner. For instance, at 37°C, CBZ solubility increased from 177 ug/mL in absence of any excipients, to ~5100 ug/mL in presence of 40% ethanol, which is ⊚30 fold increase (***Figure 2***). According to the in-vitro and the in-vivo studies, the solubility-permeability tradeoff was evident; increased ethanol levels resulted in decreased permeability. When the initial ethanol concentrations in the formulations were used for theoretical in-vivo permeability calculations, poor correlation was obtained between the experimental in-vivo permeability values and the theoretical values (***Figure 3A***). It was revealed that ~43% of the initial ethanol concentration was absorbed during the rat experiment. When these average ethanol levels were used for the in-vivo permeability calculations, excellent correlation was

achieved between the experimental results and the theoretical predictions (***Figure 3B***). According to caco-2 cells, only 14-16% of ethanol was absorbed during the experiment, and good correlation was achieved between the experimental permeability values and the theoretical calculations (***Figure 4***). These differences in ethanol absorption in rat and caco-2 cells studies can be due to differences between these in-vivo and in-vitro systems.

4. Conclusions

this work demonstrates that the solubility-permeability tradeoff exists when ethanol is used as a solubility-enabling excipient. The excellent correlation between the predicted permeability values and the in-vivo experiment values may allow to predict the formulation effect on both the solubility and the permeability and aid in the development of better oral drug formulations.

In conclusion, ethanol may significantly increase the solubility of lipophilic drugs, however it should be used with caution in oral formulations in order to prevent unnecessary permeability loss; we posit that the amount of ethanol in the formulation should be just the amount needed for the solubility/dissolution of the drug dose - and not more than that - to achieve the maximal drug absorption potential.

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