

Eutectic mixtures containing ezetimibe (ingredient pharmaceutical active): phase diagrams, solid state characterization and dissolution essays

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Eutectic and cocrystals have been studied in pharmaceutical systems as alternative to enhance materials properties, as stability, solubility and rate of dissolution[1,2]. In this context, the phase diagrams have a very important part to play, giving information about temperature and composition of the eutectic and allowing the assessment of cocrystal formation. Ezetimibe ((3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one) is an cholesterol absorption inhibitor with low aqueous solubility, which influence its therapeutic efficiency[3]. In this work, it was studied different ezetimibe/coformer solid systems, the phase diagrams, dissolution properties and hygroscopicity to assess the enhancement achieved in the final product. The coformers methylparaben (methyl 4-hydroxybenzoate), salicylic acid (2-hydroxybenzoic acid) and nicotinamide (pyridine-3-carboxamide) was chosen for showing functional groups with possible interaction with ezetimibe. The phase diagrams were built up using results of differential scanning calorimetry (DSC) analysis of the mixtures with different molar fractions of coformers. The eutectic materials were prepared by fusion and cooling of mixtures with eutectic compositions, and characterized by DSC, X-ray powder diffraction and polarized light optical microscopy. The hygroscopicity of the materials was evaluated by dynamic vapour sorption. The dissolution study was conducted with the materials in powder form, with paddle dissolution, rotating at 50 rpm, in 900 mL of aqueous buffer solution with pH 6.8. The phase diagrams demonstrated that ezetimibe formed eutectic mixtures with the three coformers, with no evidence of the formation of intermediate compounds, such cocrystals. The molar fractions at which eutectic points occur were determined by Tammann diagrams, being 0.69, 0.59 and 0.67, to methylparaben, salicylic acid and nicotinamide, respectively. The activity coefficients of ezetimibe in the mixtures were calculated and indicated a higher affinity of the drug mixed with nicotinamide, followed by the mixtures with salicylic acid and methylparaben. In regarding of the hygroscopicity, pure anhydrous ezetimibe compound uptook significant humidity above 55 % of relative humidity, due to transition from anhydrous to monohydrate. At the same temperature, eutectic materials only exhibited significant weight change above 65 % of relative humidity, demonstrating a less susceptibility to monohydrate formation. In considering the dissolution, the eutectic compounds with salicylic acid and methylparaben solubilized ezetimibe in amounts 22% higher than the pure drug. On the other hand, the eutectic compound with nicotinamide suppressed the dissolution of ezetimibe down to 56%. The results indicated the possibility of obtaining materials with enhanced properties using eutectic mixtures, with improved dissolution and a better control the hygroscopicity.

References

- [1] R. N. Costa *et al.*, New Multicomponent Forms of the Antiretroviral Nevirapine with Improved Dissolution Performance, *Cryst. Growth Des.* 2020;20(2):688–698.
- [2] J. Haneef and R. Chadha, Drug-Drug Multicomponent Solid Forms: Cocrystal, Coamorphous and Eutectic of Three Poorly Soluble Antihypertensive Drugs Using Mechanochemical Approach, *AAPS PharmSciTech.* 2017;18(6):2279–2290.
- [3] S. B. Rosenblum, Cholesterol Absorption Inhibitors: Ezetimibe (Zetia®), in *The Art of Drug Synthesis*, Hoboken, NJ, USA: John Wiley & Sons, Inc., 2006, pp. 183–196.