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Comparison of the amorphization ability of two polymorphic forms of olanzapine

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ABSTRACT

Introduction: The production of amorphous and co-amorphous (CAM) materials has been used as a procedure to overcome the poor water solubility shown by most of the drugs currently under development [1]. Ball milling has been considered to convert the crystalline state of a substance into its amorphous counterpart [2,3]. At present, the impact of the initial polymorphic form of a drug substance on its final amorphous state upon milling, has not been clearly studied. This work aims to compare the co-amorphization efficiency of two different polymorphic forms of olanzapine (OLZ; a BCS class II drug) using saccharin (SAC) as a co-former.

Materials and methods: OLZ (forms I and II) were the starting polymorphic forms to be milled with SAC (2:1 molar ratio). OLZ form I was used as received while OLZ form II was obtained from crystallisation of OLZ in dichloromethane. Ball milling was performed using 2.5 g of 3.0 mm Ø balls, for 2 h. The conversion of the crystalline states into the amorphous counterpart was monitored by calorimetry (DSC) and diffractometry (XRPD).

Results: The thermograms and the diffractograms obtained (Figure 1) have shown a clear difference between the final products of the two polymorphic forms of OLZ. XRPD peaks were less intense for OLZ form II and most representative of SAC, indicating that OLZ was indeed mostly converted into the amorphous state. On the other hand, when OLZ form I was the starting material, a richer diffractogram resulted, suggesting that a crystalline fraction of OLZ remained in the particles' network of the final product, a feature also confirmed by DSC.

Discussion and conclusions: Since OLZ form II has a higher thermodynamic energy than form I, it is not surprising that the former exhibits better amorphization ability. Thus, it is expected that either an increase on milling time, or milling speed, would enhance the co-amorphization of OLZ form I with SAC.

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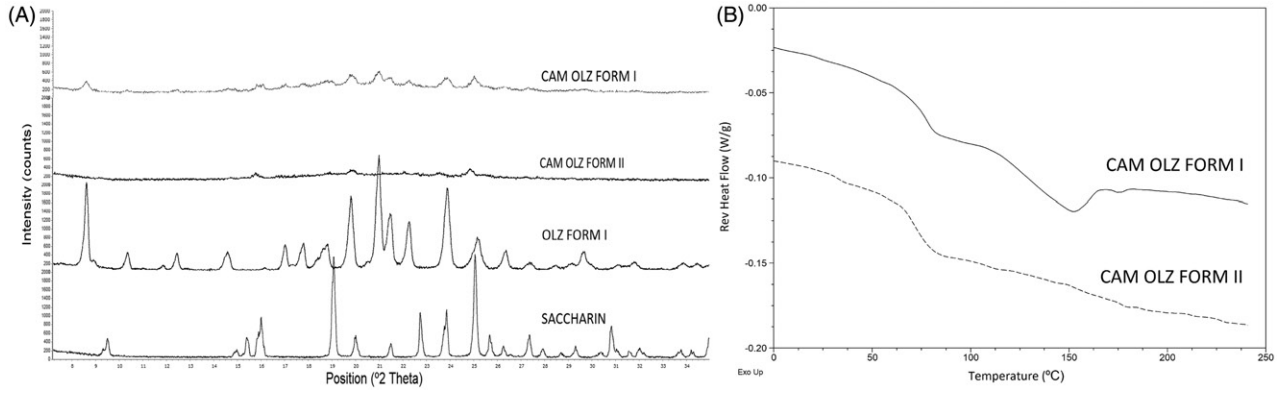

Figure 1. X-ray diffractograms (A) and DSC thermograms (B) of the different molecular entities..

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Cytotoxicity of temperature-responsive cationic diblock copolymers in human cancer and non-cancer cells lines

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ABSTRACT

Introduction: Thermoresponsive polymers have been widely investigated in modern drug delivery and gene delivery systems, due to their potential to load and release the payload by simply modifying local temperature [1]. Previous work by some of us has shown that the thermoresponsive copolymers poly(*N*-isopropylacrylamide)$_n$-*block*-poly((3-acrylamidopropyl) trimethylammonium chloride)$_m$ (PNIPAAM$_n$-b-PAMPTMA(+)$_m$) can efficiently deliver DNA and siRNA to HeLa [2] and HT1080 cells [3]. The transfection efficiency and cytotoxicity were highly dependent on the length and ratio of the two blocks (*n*:*m*) [2,3]. In anticancer therapy, such polymers may be able to deliver drugs precisely at the tumour site by local and transient thermal treatment [1]. Having this in mind, in this work, we took the first step towards expanding the scope of use of the PNIPAAM$_n$-b-PAMPTMA(+)$_m$ copolymers by investigating their cytotoxicity in human cancer cell lines and in a normal breast cell line.

Materials and methods: The copolymers (*n*:*m* ratio 48:6, 48:10 and 65:20) were dissolved in varying concentrations in cell culture medium, as described before [2] and were incubated at 37 °C with each of the tested cell lines for 6 h. After that, the medium was replaced, and the cells were incubated for 48 h/37 °C. The viability of cells was measured by the MTT cytotoxicity assay. Untreated cells were used as negative control (representing 100% viability). *Cell lines:* HeLa (cervical cancer), HCC1806 (breast cancer) and MCF10A (non-tumorigenic breast epithelial cell line).

Results: In this preliminary study the cytotoxicity of the PNIPAAM$_n$-*b*-PAMPTMA$_m$(+) copolymers was shown to be dependent on the polymer concentration, *n*:*m* ratio and cell line. MCF10A cells were very tolerant to the presence of the copolymer 48:6, even at the highest concentration (Figure 1), followed by HeLa and HCC1806.

Discussion and conclusions: The low toxicity shown particularly for the non-tumorigenic cell line but higher toxicity towards the cancer cell lines makes the tested copolymers highly appealing as drug carriers in anti-cancer therapy.

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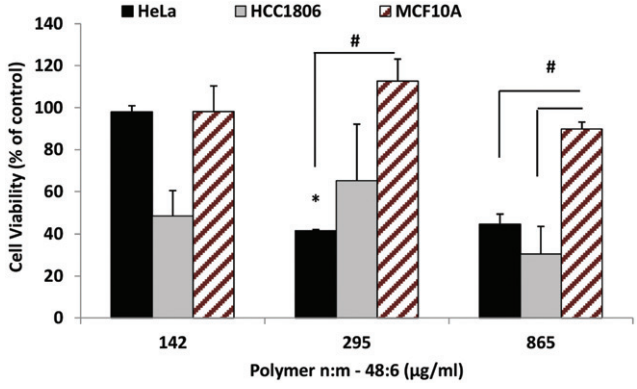

Figure 1. Cell viability in the presence of the 48:6 (n:m) copolymer. Mean ± SD. Comparisons were made at the same cell line at the immediately precedent concentration (*$p < 0.05$) and for the same concentration between lines (#$p < 0.05$).