Non-PAMAM amino acids-modified dendrimers nanoparticles for enhancing water-solubility of insoluble bioactive molecules: our state of the art

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ABSTRACT

Water-solubility is essential for GIT absorbability or parenteral administration of drugs, therefore it is a key parameter to achieve the systemic drug concentration necessary for an effective therapeutic activity. Unfortunately, low aqueous solubility is the major problem with bioactive chemical entities (BCEs), in fact, more than 40% BCEs developed in pharmaceutical industry are practically water-insoluble. As a consequence, great are the research efforts focused on the development of new techniques aiming at enhancing it. Toxic excipients and harmful solubilizing agents were also extensively used for solubilizing and delivering non water-soluble drugs, despite the resulting unpleasant side effects complained of by patients. Nowadays, safer strategies, such as drugs physicochemical modifications or particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant and complexation are being exploited. As far as what regards dispersion/complexation techniques, nanoparticles, including dendrimers, are intensely utilized for this purpose, thus in parallel achieving drugs protection from early degradation, more efficient target delivery into cells and tissues and lower systemic toxicity. Synthetic thiocarbamate (O-TC **1)** (Fig. 1) is a non-nucleoside HIV-1 reverse transcriptase inhibitor [1] while Ellagic Acid (EA **2**) (Fig. 2) is a polyphenol present in some fruits, nuts and seeds endowed with strong antioxidant, anti-inflammatory and other several healthy properties. Unfortunately, both of them are practically insoluble (Table 1), non orally bioavailable, non parenteral administrable, then non usable for therapeutic purposes in their free forms.

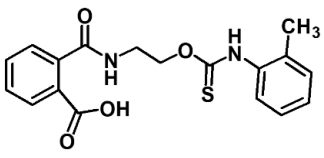

Fig. 1: *Structure of O-TC **1***

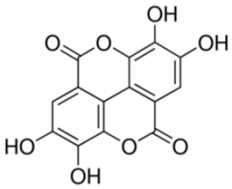

Fig. 2: *Structure of EA **2***

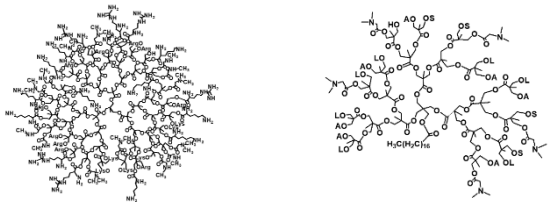

Fig. 3: *Examples of hydrophilic (left) and amphiphilic (right) dendrimers structure*

During the last year, these problems have been addressed and successfully resolved by us, and in this communication, the reached promising outcomes have been summarized and the current state of the art provided. Afar from commercially high cytotoxic PAMAM, five non cells-damaging amino acid-modified hydrophilic (**3**, **4**) [2] and amphiphilic (**5**-**7**) [3] dendrimers (Fig. 3) have been synthetized and then used as polymer nano-containers to improve **1** and **2** water-solubility. Five (**8**-**12**) [4] and two (**13**, **14**) [5] structurally different drugs-loaded nanodispersions (DPXs) were obtained respectively. The structures were confirmed by FT-IR and NMR analysis and all the samples have resulted in being endowed with very good Drug Loading (DL %). Compound **1**, totally insoluble except for in highly diluted DMSO when free, once entrapped in dendrimers, shown to be well soluble both in water and in ethanol. In the case of **2**, water-solubility was increased even up to 1000 times compared to the free form. For the prerogatives demonstrated in the performed routine analyses, the prepared DPXs could be considered eligible for biomedical and therapeutic applications thus allowing to exploit **1** and **2** pharmacological properties.

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