**Physical formulation approaches for improving aqueous solubility and bioavailability of ellagic acid: complexation with cyclodextrins and solid dispersions formation**

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Ellagic acid (EA) is one of the most studied polyphenolic compounds due to its numerous promising therapeutic properties. However, this therapeutic potential remains difficult to exploit owing to its unfavorable physicochemical properties such as low solubility and low permeability resulting in low oral bioavailability (BCS IV). This bioavailability can be improved by increasing solubility. The aim of our study was therefore to increase the aqueous solubility and consequently the bioavailability of EA to allow its use in human therapy.

Complexation of EA with cyclodextrins and solid dispersion were used as two different approaches to increase the solubility. For the complexation, a phase solubility study was performed different cyclodextrins (β-CD, γ-CD) according to the method of Higuchi and Connors. Based on these EA/cyclodextrin solubility data, complexes were prepared and freeze-dried. The obtained freeze-dried products were characterized by Fourier transform infrared spectroscopy (FTIR) and their spectra compared to those of the starting materials.

In parallel, the solid dispersions were prepared using three polymers, namely Eudragit® EPO, Soluplus® and Kollidon® VA 64. Physical mixtures composed of 5% weight/weight of EA and 95% of polymer were extruded using a twin screw hot-melt extruder. The extrudates obtained were characterized by *in vitro* dissolution tests, homogeneous assays and X-ray diffraction.

The results showed that the complexation of EA by cyclodextrins increased its solubility. Indeed, the apparent solubility of EA resulting from its complexation with cyclodextrins, was 9.92 times and 2.98 times its actual solubility with γ-CD and β-CD respectively. With solid dispersions, we obtained an increase of the dissolution rate as well as of the apparent solubility of ellagic acid. Indeed, after 15 min of dissolution test, the extrudates gave dissolution rates of 96.25 ± 5.30%, 42.5± 0.70%, and 41.50± 4.23% respectively with Eudragit® EPO, Soluplus® and Kollidon® VA 64 while pure ellagic acid gave 1.56 ± 0.16%. In terms of increase in solubility of EA, the maximum apparent solubility obtained through the dissolution test with Kollidon® VA64 was 8 times its real solubility, with Soluplus® it was more than 10.4 times and with Eudragit® EPO 20 times.

The two approaches of solubility increase used in our study are thus promising in term of improvement of the solubility of EA. Moreover, a combination of the two approaches will be consider to evaluate a synergy of action in term of increase of the solubility of EA by the formation of ternary solid dispersion.