

## EFFECT OF MIXING IN THE PREPARATION OF DOXORUBICIN-LOADED CYANOACRYLATE NANOPARTICLES VIA SOLVENT DISPLACEMENT

Barbara Stella<sup>1</sup>, Sara Bolognesi<sup>1</sup>, Federica Lince<sup>2</sup>, Daniele L. Marchisio<sup>2</sup>, Antonello A. Barresi<sup>2</sup>,  
Franco Dosio<sup>1</sup>

<sup>1</sup>Dipartimento di Scienza e Tecnologia del Farmaco, Università degli Studi di Torino, Via P. Giuria 9, 10125 Torino, Italy.

<sup>2</sup>Dipartimento di Scienza dei Materiali e Ingegneria Chimica, Politecnico di Torino, Corso Duca degli Abruzzi 24, 10129 Torino, Italy.

The solvent displacement method involves three main steps to obtain nanoparticles: dissolution of both the polymer and the drug into a solvent, mixing of the obtained solution with the anti-solvent, and elimination of the solvent through evaporation.<sup>1</sup> Mixing leads to rapid diffusion of the solvent into the anti-solvent and spontaneous particle formation. Particle formation is extremely rapid and therefore mixing must be very fast: for this reason special efficient continuous mixers must be used, such as Confined Impinging Jets Reactors (CIJR),<sup>2,3</sup> in which two solutions of solvent and anti-solvent are mixed in a very small volume in the center of a mixing chamber, where owing to collision and impingement of the two jets, turbulent kinetic energy is generated and then quickly dissipated. This reactor generally leads to high mixing efficiencies, which allows production of very small particles.

In this work poly(methoxypolyethyleneglycol cyanoacrylate-co-hexadecyl cyanoacrylate) (P(MePEGCA-co-HDCA))<sup>4</sup> nanoparticles formation in CIJR by solvent displacement was investigated. Poly(hexadecyl cyanoacrylate) (PHDCA) nanoparticles were also prepared. Acetone and tetrahydrofuran (THF) were used as solvents, whereas water was used as anti-solvent. The incorporated active principle was doxorubicin (DOX). The effect of the different operating conditions (initial polymer and drug concentration, anti-solvent to solvent ratio, mixing rate and solvent type) on the final nanoparticles characteristics (mean particle size, zeta potential, morphology and stability) was investigated.

The results showed that the effect of the flow rate (FR) (and therefore of the mixing rate) and of the initial P(MePEGCA-co-HDCA) concentration on the final mean particle size is quite important. The effect of the FR is such that, by employing the very same initial solutions and by increasing the FR from 3 to 120 ml/min, a reduction of the mean particle size from 350 to 80 nm is detected. When the FR is increased, better mixing efficiencies in the reactor are achieved, generating higher super-saturation levels and promoting the nucleation of smaller particles.

If the initial polymer concentration is increased, particles become bigger and their size changes from less than 225 nm up to 300 nm. The zeta potential does not change much in sample prepared under different mixing rates. It is also possible to detect a correlation between FR and standard deviation that seems to exist for size and also for zeta potential. Also the solvent type (i.e., acetone versus THF) and the anti-solvent to solvent ratio influence the final mean particle size, which increases as the anti-solvent to solvent ratio is increased from 1 to 8. Nanoparticles obtained by employing acetone as solvent are smaller. The presence of DOX (drug loading of about 4%) induces the formation of bigger particles, suggesting the incorporation of the drug in the polymeric matrix.

Morphological analyses SEM and FESEM showed that nanoparticles have a spherical shape, with a size in agreement with the nanosizer measurements.

Drug release and *in vitro* tests (i.e. antitumoral activity, confocal microscopy) are in progress.

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