Tramadol Hydrochloride Released from Lipid Nanoparticles: Studies on Modelling Kinetics

Elena Sánchez[a], Helen Alvarado[a,b*], Prapaporn Boonme[c], Guadalupe Abrego[a,b], Tatiana Andreani[d,e], Monica Vazzana[f], Joana F. Fangueiro[b], Catarina Faggio[f], Carla Silva[g], Sajan José[h], Antonello Santini[i], María Luisa Garcia[a], Ana C. Calpena[b] Amélia M. Silva[d,e], Eliana B. Souto[j*]

[a] Department of Physical Chemistry, Faculty of Pharmacy, University of Barcelona, Av. Joan XXIII s/n, 08028 Barcelona, Spain
[b] Department of Biopharmacy and Pharmacology, Faculty of Pharmacy, University of Barcelona, Av. Joan XXIII s/n, 08028 Barcelona, Spain
[c]Faculty of Pharmaceutical Sciences, Prince of Songkla University, Thailand
[d]Department of Biology and Environment, University of Trás-os Montes e Alto Douro, Portugal;
[e]Centre for Research and Technology of Agro-Environmental and Biological Sciences, Portugal;
[f]Department of Biological and Environmental Sciences, University of Messina, Italy;
[g]Center for Nanotechnology and Smart Materials, Portugal;
[h]Department of Pharmaceutical Sciences, Mahatma Gandhi University, India;
[i]Department of Pharmacy, University of Napoli, Italy;
[j]Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Coimbra

*E-mail address corresponding author: hl_alvarado@yahoo.com; ebsouto@ff.uc.pt

Keywords: tramadol hydrochloride, HPLC, lipid nanoparticles, kinetic model

A reverse-phase (RP) high performance liquid chromatography (HPLC) method was developed according to the International Conference on Harmonisation (ICH) guidelines, for the determination of tramadol hydrochloride (THC) from lipid nanoparticles (LNs). THC is an opioid analgesic drug, mainly acting on the central nervous system (CNS) and structurally related to codeine and morphine, but clinically 10-fold less potent than codeine and 6000-fold less than morphine. It was developed in 1970s and is currently in use for the management, treatment and relief of moderate to severe pain conditions. A method for the preparation of THC standard and N1,N1-dimethylsulfanilamide (used as the internal standard) has been described. HPLC analysis was performed on a 250x4 mm chromatographic column with LiChrospher 60 RP-selectB 5-µm (Merck), using acetonitrile:0.01 M phosphate buffer, pH 2.8 (3:7, v/v) as mobile phase. Fluorescence detection was done at 296 nm (THC) and at 344 nm (N1,N1-dimethylsulfanilamide). THC-loaded LNs dispersions were produced by hot high pressure homogenization technique, using Compritol® 888ATO as solid lipid, stabilized with 3% (w/w) Phospholipon® 80H and 1% (w/w) Tyloxapol® as surfactants. Particles ranging between 79.4±0.3 and 144.6±14 nm in size were obtained, with a mean zeta potential of -10.2±1.2 mV. Four kinetic models (i.e., zero order, Higuchi, Baker-Lonsdale and Korsmeyer–Peppas) were selected to fit the data to describe the THC release profile from LNs. The *in vitro* release profile of THC from LNs was compared with that from the commercial oral suspension (Tramal®), in pH 6.8 phosphate buffer. Commercial THC suspension depicted a 100% release in the first hour; whereas for LNs, a biphasic sustained release profile was observed. According to the obtained R^2 values, Korsmeyer-Peppas model was reported as the best fit modelling kinetic

profile for THC release from LNs. The recorded n = 0.63 value typical for anomalous non-Fickian transport is in agreement with the biphasic mechanism of drug release from LNs.