OP-30

DOI: 10.14232/syrptbrs.2020.op30

Nano-crystalline suspensions of novel pyrazoloquinolinones ligand (DK-I-56-1): physicochemical and in vivo pharmacokinetic and behavioural characterization

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Very low solubility in water and oils (<10 μg/ml) of DK-I-56-1 (7-methoxy-2-(4-methoxy-d3-phenyl)-2,5-dihydro-3H-pyrazolo[4,3-c]quinolin-3-one), the new drug candidate from the group of deuterated pyrazoloquinolinones [1], was the reason for investigation of nano-crystalline suspensions (nanosuspensions) as prospective carriers. Nanosuspensions are dispersions of nanocrystals with submicron size stabilized by different surfactants and/or polymeric stabilizers [2]. In this research, formulation and comprehensive characterisation of DK-I-56-1 nanosuspensions were carried out. Nanosuspensions stabilized by polysorbate 80 alone or in combination with poloxamer 188, poloxamer 407 or d-α-Tocopheryl polyethylene glycol 1000 succinate were prepared by small scale media milling technique. All formulations had particle size 208.7 – 250.6 nm, polydispersity index <0.250 and zeta potential around -20 mV, and were stable for three weeks. According to thermal and X-ray diffraction analysis DK-I-56-1 remained in crystalline state in all samples. Results from biodistribution studies in mice after intraperitoneal administration showed high plasma DK-I-56-1 levels after nanosuspension administration (AUC values for nanosuspension, suspension and solution: 6770.35±770.69; 966.01±58.10; 10228.58±1037.23 ngh/ml, respectively). Brain availability was higher after nanosuspension compared to solution, while concentration profile after suspension showed bimodal characteristics. In *in vivo* behavioural (spontaneous locomotor activity) tests hyperlocomotion was observed after nanosuspension administration compared to saline or placebo ($F(2,31)=7.126$, $p<0.01$), while placebo was not behaviourally active compared to saline ($p=0.289$). In conclusion, DK-I-56-1 nanosuspensions with short term stability could be prepared and should be investigated as promising carrier for preclinical investigation.

References:

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