BIOAVAILABILITY IMPROVEMENT OF POLYMYXIN B BY CALCIUM ALGINATE/CHITOSAN MICROPARTICLES

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Polymyxin B (PMB) is an antibiotic rapidly bactericidal against Gram-negative bacteria but, due to systemic toxicity (polymyxins bind to the cell membrane and alters its structure making it more permeable) and poor bioavailability after oral administration, polymyxin B is only used topically. Oral absorption of drugs with poor bioavailability is possible via translocation by Peyer's patches (PP) M cells thanks to their ability to take up inert particle sized less than 5 μm. Aim of the study was to evaluate *in vitro* and *in vivo* the activity and the toxicity of a micro-system loaded with therapeutic dosages of polymyxin B. The designed calcium alginate/chitosan microparticles were spherical in shape, in size, fluorescent and suitable to be taken up by PP. *In vitro* cytotoxicity MTT test performed on Vero cells failed owing to the micro-particles which are not suitable for this test. *In vivo* experiments were performed on Sprague Dawley rats (220±20g) divided into four groups and treated by a single intragastric administration as follows: Fasted rats treated with PMB solution (group 1), fed rats treated with PMB solution (group 2) , fed rats treated with unloaded micro-particles (group 3), fed rats treated with PMB loaded micro-particles (group 4). Results from"*in vivo*" experiments did not confirmed PMB LD_{50} reported in literature: 790mg/Kg resulted lethal within 30 minutes for fasted and fed rats: macroscopical *post mortem* examination revealed severe intestinal hemorrhages. Lower dosages were tested and the highest percentage of death was observed in fasted rats. 300mg/kg was the right PMB LD_{50} detected on fed rats. PMB 125mg/Kg both in water solution and in micro-system water suspension was administered by oral gavage to rats afterwards housed in metabolic cages, monitored (survival, behaviour, clinical signs) through 72h. No rats from group 2 died within 24 hours however, dyspnoea and suffering signs were observed. Stomachs exicised from all the rats were inflated. No rats from group 3 showed signs of suffering or died just confirming the safety of the system. All the rats treated with PMB loaded particles (group 4) were still alive over 24 h without any appreciable behavioural sign of acute toxicity. Urine, blood and intestine samples were collected at 6 and 24, 48 and 72 hours to detect PMB level. Peyer's patches were examined by fluorescence confocal microscopy and fluorescent particles were found only inside patches from group 4. Microbiological test of PMB urine and serum levels confirmed the antibacterial activity of the system and. In conclusion, the study revealed that the micro-particles allow oral administration and absorption of PMB with the advantage of a reduced toxicity.