Effect of different excipients and processing conditions on casein micellar formulation for children

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Purpose: Investigation of the potential of casein micellar formulations as drug vehicles in pediatrics.

Methods: Several casein (CN) formulations were prepared, by the addition of cryoprotectant (mannitol or lactose, 1%w/v), crosslinker carbodiimide (EDC, 0.03M, during 24h) or genipin (GP, 0.03M, during 24h) and/or paracetamol (PC). The dispersions were freeze (-80°C/24h)-dried (-50°C/0.035mbar/12h) (FD) and stored at room temperature (3month). Micelles were characterized for shape (TEM), particle size, zeta potential and encapsulation efficiency (EE). FTIR spectra (4000–400cm^{-1}) and thermograms (15-200°C) were obtained. The release of PC from uncrosslinked and crosslinked micelles was compared in phosphate buffered saline (PBS) pH 7.4. PC was quantified by liquid chromatography (phosphate buffer, 0.01M NaH_2PO_4/pH5.8 and acetonitrile gradient).

Results and Discussion: Crosslinking promoted more compact micellar structure for CN-EDC (80±13nm) but larger micellar size (205±8nm) for CN-GP compared to control CN samples (178±22nm). The addition of cryoprotectant resulted in small micelles (80-90nm), whereas PC loaded micelles increased the average micellar size after FD. The EE was approximately 30% and remained stable during FD in uncrosslinked casein, but dropped down to 14% in FD GP-CN samples. All micelles presented a negative surface charge (-5 to – 8 mV). Thermograms of casein failed to show thermal events and PC was not detectable in the CN micelles due to the absence of an endotherm (169°C, form I), suggesting its existence in the amorphous state. The second derivative spectra of crosslinked CN displayed altered stretching frequencies and peak shifts, compared to uncrosslinked casein, in the amide II and III region which could be attributed to potential intramolecular cross-linking. Significantly retarded release was found for the PC entrapped into the casein micelles, particularly the ones with EDC and lactose, as compared to the free drug control. All micelles were stable over 3 months of storage, except for GP crosslinked samples.

Conclusions: Casein can be a vehicle for the delivery of drugs in pediatrics, following a straightforward production process, namely with retarded release of the encapsulated drug. Furthermore the study also provided information on the use of carbodiimide as a crosslinker for casein.