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Preparation and *in-vitro* evaluation of Meloxicam co-ground mixtures

Aly Nada
Kuwait University, Kuwait

Meloxicam is a non-steroidal anti-inflammatory drug of the oxicam class, used to relieve the symptoms of dental pain, arthritis, primary dysmenorrhea, fever and as an analgesic, especially where there is an inflammatory component. Meloxicam inhibits cyclooxygenase (COX) synthesis. This enzyme is responsible for converting arachidonic acid into prostaglandin H2. This is the first step in the synthesis of prostaglandins, which are mediators of inflammation. Meloxicam has been shown, especially at its low therapeutic dose, selectively to inhibit COX-2 over COX-1. The co-grinding technique, unlike the other solid dispersion techniques, was economically and environmentally desirable. In co-grinding approach, the use of toxic organic solvents could be easily avoided. Therefore, it was suitable for industrial manufacture on a large scale. Co-grinding of poorly water soluble drug (Meloxicam) particles with different hydrophilic polymers like PEG and / or PVP-K25 resulted in the formation of amorphous powders having enhanced drug solubility and dissolution properties , even if much smaller amount of hydrophilic polymers were used (MLX/hydrophilic polymers =1:1, w/w). According to percentage of drug dissolved, dissolution rate of MLX – PEG co-ground binary mixture prepared by ball mill or vibrational mill > MLX – PEG – PVP co-ground ternary mixture > MLX – PVP co-ground binary mixture > MLX – polymer physical mixture > MLX alone. As regards to the grinding techniques, co-ground mixtures prepared with ball mill has a relatively higher dissolution rate than those prepared with vibrational mill for all of the selected polymers at all of the employed ratios. An increase in the concentration of carrier in the co-ground blends resulted in an increase in the dissolution rate of MLX. The enhancement of dissolution of MLX from co-ground mixtures could be due to the reduction of crystalline nature of the drug in co-ground mixtures. Among all the prepared mixtures in this study, co-ground mixture of MLX and PEG in 1:4 ratio by ball mill showed the best results in terms of extent and rate of dissolution in water and phosphate buffer. This effect was not only due to particle size reduction, but also loss of crystalline nature of the drug during co-grinding. DSC and PXRD studies indicated that crystalline nature of drug was reduced after co-grinding with PEG and / or PVP as compared to their corresponding physical mixtures. SEM images showed that particle size of MLX was reduced after co-grinding with hydrophilic polymer PEG using ball mill.

alynada@hsc.edu.kw

Multifunctional polymeric micelles for the simultaneous delivery of siRNA and chemotherapeutic agents: A promising strategy to reverse the drug resistance in the treatment of cancer

Giuseppina Salzano
Northeastern University, USA

Since its discovery, small interfering RNAs (siRNA) have quickly crept into the biopharmaceutical research as a powerful tool for the treatment of different human diseases based on altered gene-expression. Despite promising data from pre-clinical studies, concrete hurdles, still need to overcome to bring therapeutic siRNAs in clinic. With this in mind, we have reversibly modified siRNA with a phosphothioethanol (PE) portion via a reducible disulfide bond and incorporated the resulting siRNA-S-S-PE conjugate into nanosized polyethyelene glycol 2000-phosphatidyl ethanolamine (PEG2000-PE)-based polymeric micelles (PM). Then, we successfully co-incorporated in the same PM, an anti-survivin siRNA-S-S-PE conjugate and chemotherapeutic agent such as paclitaxel (PXL) for combined therapy. The developed nanopreparation showed high colloidal stability, high incorporation efficiency of both active agents, and small particle sizes compatible for parenteral administration. In an animal model of cancer, the micelles accumulate in distal tumors and delivered anti–survivin siRNA and PXL in sufficiently high amounts to mediate a potent and specific survivin downregulation and to improve anticancer activity as compared with single agents. In addition, survivin downregulation by anti–survivin siRNA/PXL PM mediated the sensitization of a resistant ovarian tumor to non-effective doses of PXL. Compared to conventional systems for siRNA delivery, we suggested a new type of platform that can respond to local stimuli, such as high levels of reductase in cancer cells, and release the siRNA free and active at the desired site. Moreover, the developed PM are suitable to incorporate different type of active agents for combined therapy.

g.salzano@neu.edu