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Expression of antimicrobial peptide Hcap18/LL-37 following non-viral delivery of plasmid DNA encoded by CAMP gene in human fibroblasts and keratinocytes

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Since the incidence of breast cancer increases dramatically all over the world, the search for effective treatment is an urgent need. Metformin (MET) has demonstrated anti-tumorigenic effect both *in vivo* and *in vitro* in different cancer types. The present work was designed to examine on molecular level the mode of action of MET in mice bearing Solid Ehrlich Carcinoma (SEC) and to evaluate the use of MET in conjunction with doxorubicin (DOX) as a combined therapy against SEC. Ehrlich ascites carcinoma cells were inoculated in 60 female mice as a model of breast cancer. The mice were divided into four equal groups: Control tumor, MET, DOX and co-treatment. MET (15 mg/kg) and DOX (4 mg/kg) were given i.p. for four cycles every five days starting on day 12 of inoculation. The anti-tumorigenic effect of MET was mediated by enhancement of adenosine monophosphate protein kinase (AMPK) activity and elevation of P53 protein as well as the suppression of nuclear factor-kappa B (NF-5B), DNA contents and cyclin D1 gene expression. MET and DOX mono-treatments exhibited opposing action regarding cyclin D1 gene expression, phosphorylated-AMPK (PAMPK) and NF-5B levels. Co-treatment markedly decreased tumor volume, increased survival rate and improved other parameters compared to DOX group. In parallel, the histopathological findings demonstrated enhanced apoptosis and absence of necrosis in tumor tissue of co-treatment group. MET proved chemotherapeutic effect which could be mediated by the activation of AMPK and related pathways. Combining MET and DOX, which exhibited different mechanisms of action, produced greater efficacy as anticancer therapeutic regimen.

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Optimization of the parameters of spherical agglomeration method

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In the industry area, direct compression is one of the most important techniques for the formulation of solid form drugs. For this, the active agent, so as our target product should possess appropriate parameters for example increased flow rate generated by large-size (>100 □m) spherical or nearly spherical (roundness < 1.5) crystals or crystal agglomerates. For improving the morphology, spherical crystallization techniques can be used, like typical and non-typical ones. In case of non-typical methods (like antisolvent crystallization, cooling crystallization or combined method) mainly the physico-chemical parameters are changed. Typical methods (like quasi emulsion solvent diffusion method) use three solvents. From our previous work it became clear that spherical agglomeration is suitable for improving the morphology of ambroxol hydrochloride (AMB-HCl). This work aims at the optimization of the parameters of this method. For this, a factorial design was applied and then the results were evaluated with STATISTICA for Windows program. The critical parameters were as follows: agitation type and time, temperature differences between the solvent (dimethyl sulfoxide) and the antisolvent (ethyl acetate), composition of the solvent system (solvent/antisolvent ratio). The average size, aspect ratio and roundness of the products were analysed by LEICA Q500 MC Image Processing and Analysis System, then the ones with proper morphology were chosen for further experiments. With an additional factorial design, effects of other parameters were examined such as saturation rate and feed rate of AMB-HCL solution. The products were also examined by an individually-developed hardness test. Four products were proved to possess suitable morphology compared to the target product. The application of horizontal shaker with shorter mixing times and lower temperature differences had a positive impact on the morphology of AMB-HCl. The hardness of the products was large enough to keep the spherical particles stable.

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