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A design of experiment study to engineer the properties of chitosan nanoparticles as matrix to sustain drug release across orally disintegrating tablets

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Background: sustained release orally disintegrating tablets (SR-ODT) are dosage form, that fully disintegrate within the oral cavity and produce a long onset action, SR-ODT have proven their place over conventional tables, especially among pediatrics, geriatrics, and psychiatrics and for people suffering from dysphagia.

Methods: A design of experiment (DoE) was first performed using Minitab to determine the effect of five independent variables on three dependent responses when producing the nanoparticles using ionotopic gelation. The variables studied are (tripolyphosphate concentration TPP, Chitosan concentration CS, acetic acid concentration, Chitosan: tripolyphosphate and stirring time) and the responses are (particle size, surface charge and encapsulation efficiency). A formulation with optimum particle size, surface charge and encapsulation efficiency was prepared and further coated with polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and polyethylene co-acrylic acid (PEAA). The coated nanoparticles were incorporated into ODTs tablet matrix made of lactose monohydrate and low substituted hydroxypropyl cellulose and in vitro release studies were investigated. Promethazine (PMZ) was used as a module drug for this study.

Results: Minitab studies revealed that the nanoparticles' particle size is affected by most of the independent variables. For instance increasing the concentration of TPP was associated with an increase in the particles size and this is possibly because of the stiffening of the cross linking bonds between TPP and CS. For encapsulations efficiency, drug concentration and the ratio between CS:TPP were the two main variables affecting the EE. The optimized nanoparticles showed particle size of 153.8 ± 14 nm, surface charge of 31.4 ± 0.9 mV and encapsulation efficiency of $99.7 \pm 0.06\%$. The DSC showed that PMZ was solubilized within chitosan nanoparticle, whereas SEM images indicated that all the samples were spherical in shape with smooth surface and had similar size to that measured by DLS. After coating and dispersing into the tablets' matrices, the tablets were evaluated to determine the friability, disintegration time and tensile strength. All tablets were at an appropriate friability (less than 1%) and had tensile strength above 2.5 N/mm². Besides, all the tablets managed to disintegrate within 40 seconds. The drug release profile was studied in 0.01M HCL solution. Tablets containing PVP and PEG nanoparticles managed to sustain the drug release as less than 50% of the drug was released over 24hr. On the other hand, non-coated and PEAA showed a faster rate of release, as for PEAA 60 % of the drug was released within the 24hr and 75% of the drug was released from the non-coated nanoparticles.

Conclusions: based on the results provided from this study, nanoparticles could be used to sustain the drug release across ODTs.

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