APPLYING QUALITY BY DESIGN APPROACH IN FLUPHENAZINE DECANOATE NANOEMULSION OPTIMIZATION USING DESIGN EXPERT®

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Background:
In the development of pharmaceutical formulations, there are numerous variables that contributes to a highly variable final product. Various active pharmaceutical compounds with variable excipients combined withs several methods lead to a poor-quality pharmaceutical formulation. To control the pharmaceutical products quality, the United States Food and Drug administration (USFDA) inculcated quality by design (QBD) approach in regulatory practice and pharmaceutical development (2009). QBD refers to understanding various parameters and their interactions to obtain the desired quality. Nanoemulsion (NE)is a colloidal system of nanoscale droplets dispersed in continuous phase and stabilized by surfactants and co-surfactants. Nanodroplets are formed under mechanical extrusion or high shear stress. Due to the various parameters that contribute to NE formulation, QBD was applied to optimize the formulation.

Methods:
The NE formulation was optimized using a 4-factor, 5-level central composite design (CCD) with Design Expert Software version 11 (State-ease, Minneapolis, USA). Oil amount (mg), surfactant to oil ration (SOR), co-surfactant amount(mg) and sonication time(m) were used as factors in the optimization process. Two responses were then observed, namely droplet size and polydispersity index (PDI). Twenty-eight formulations were suggested from the software and their responses of the dependent variables were recorded.

Results:
The results revealed that the droplet size and PDI of FLU-D NE optimization process followed the quadratic models. The F-values of droplet size analysis was 11.24. With respect to the PDI analysis, the F-values was found to 9.35. The *p-value* of<0.001 was found in the case of droplet size and PDI analysis, indicating that the parameters exhibited significant effects on the droplet size and PDI of FLU-D NE. In terms of sonication time, increasing the sonication time from 5m to 15m did not have a significant effect ($p>0.05$) on both dependent variables. Further, SOR within the pre-selected range didn`t show a significant effect on Droplet size and PDI, (*P value*=0.6996) for droplet size and (*P value=0.1772*) for PDI. On the other hand, oil amount has a significant effect ($p=0.01$) on the droplet size. Also, co-surfactant amount was found to have a significant influence on the droplet size and PDI of FLU-D NE ($p<0.05$). Based on the interactions between different parameters and their effect on the final formulation, the software suggested a formulation to match the desired responses. The suggested formulation was tested, and responses were recorded. Responses of the suggested formulation were within the desired ranges.

Conclusions:
From the response surface plots it can be concluded that with respect to parameters observed. QBD approach showed a significant role in time saving and successful development of NE, matching the established target product profile.