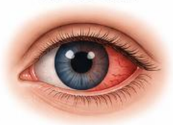
A DESIGN OF EXPERIMENTS PREDICTIVE MODEL DEVELOPMENT IN THE FORMULATION OPTIMIZATION OF CORTICOSTEROID NANOCRYSTALS FOR OPTHALMIC DRUG DELIVERY

P.S. Londono[1]*, K.K. Hartanto[1], L. Lopez-Vidal[1], L. Kalshoven[2], B. Mezghrani[2], F. Barros[2], M.G. Bordon[3], and A.J. Paredes[1]
[1]School of Pharmacy, Queen's University Belfast, BT1 1NN Belfast, UK
[2]EUROAPI, Research & Development Department, 4 La Paterie - 63480 Vertolaye, France
[3]Karlsruhe Institute of Technology, 76131 Karlsruhe, Germany
*e-mail: plondonoruiz01@qub.ac.uk

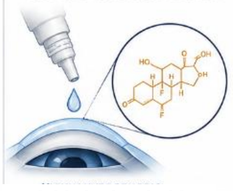
INTRODUCTION

INFLAMMATORY EYE DISEASE



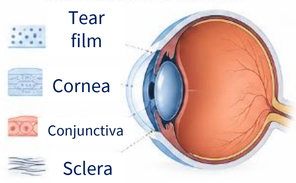
15% Of preventable blindness

First Line of treatment: topical corticosteroids



Highly hydrophobic substances [1]

Physiological barriers that limit drug absorption

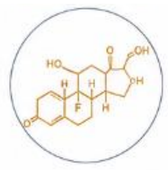


Only 5% Bioavailability

From conventional eye drops [2]

OUR SOLUTION

Corticosteroids



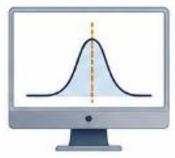
Design of experiments (DoE) approach

Optimized nanocrystals (NCs)

Increased dissolution rate

Higher saturation solubility [3]

Predictive model to control particle size

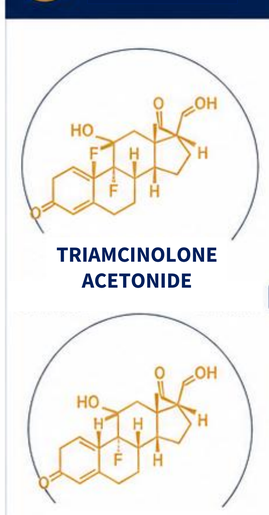


Objective

To develop a Design of experiments (DoE) optimized triamcinolone acetonide and prednisolone nanocrystals (NCs) formulation

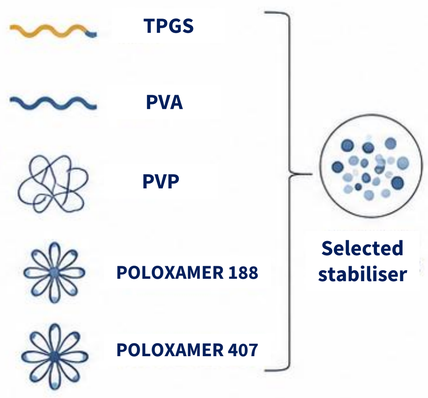
METHODS

1 DRUGS



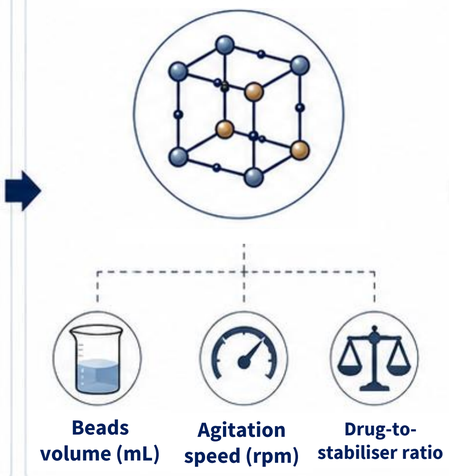
2 STABILISER SCREENING

Screening of stabilisers to select the one producing the smallest particle size



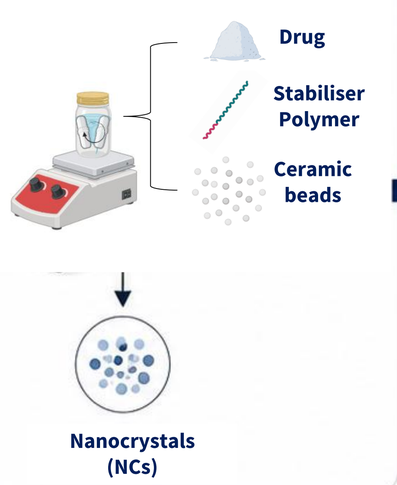
3 DoE RESPONSE SURFACE MODELLING

Optimization of particle size studying the effects of milling variables



4 TOP-DOWN NCs PRODUCTION

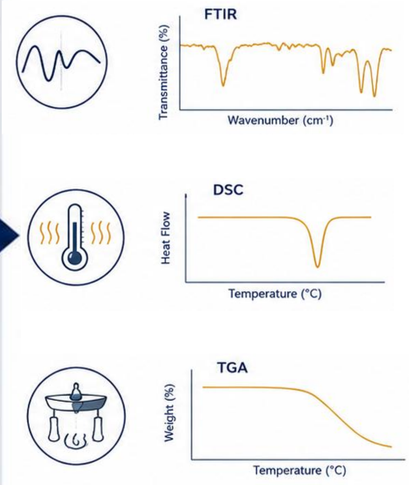
Wet Media Milling at lab scale



5 PARTICLE SIZE MEASUREMENT

Hydrodynamic diameter measured by DLS

6 NCs CHARACTERIZATION



SCREENING & DESIGN OF EXPERIMENTS (DoE) MODELLING RESULTS

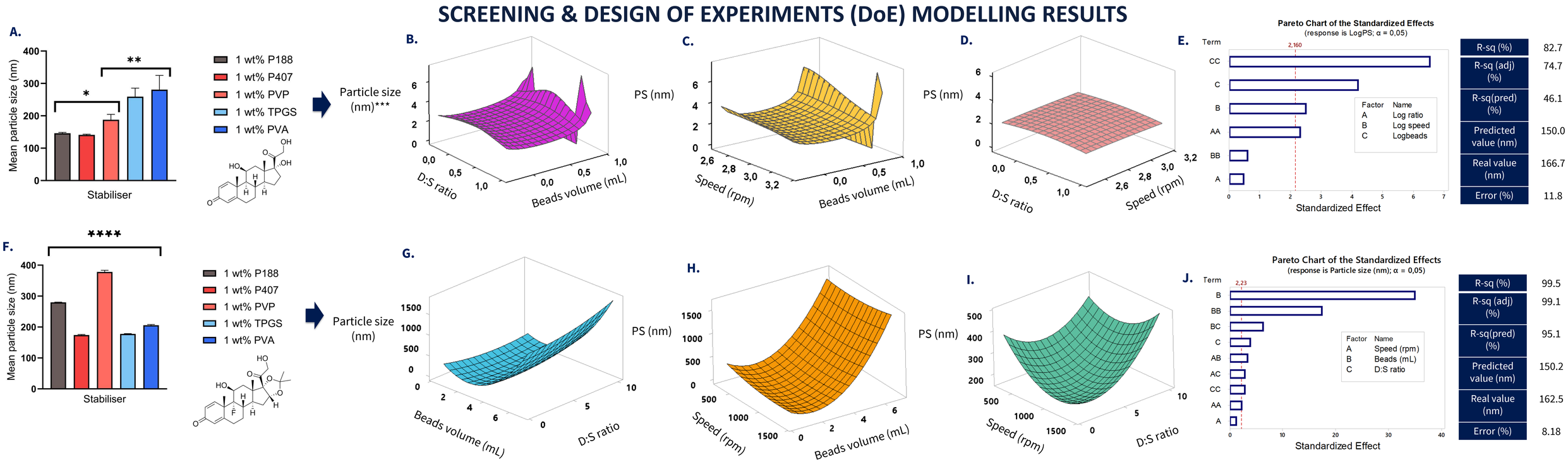


Figure 1. Screening and design of experiments (DoE) modelling results for nanosuspension optimisation. (**A–E) Prednisolone: (A)** Effect of stabiliser type on mean particle size at 1 wt%. *One-way ANOVA followed by Tukey's post hoc test indicated no statistically significant differences in particle size among formulations containing P188, P407, and PVP (α: 0.05).**Similarly, no significant differences among formulations containing PVP, TPGS, and PVA (α: 0.05); **(B–D)** response surface plots illustrating the effects of bead volume, agitation speed, and drug-to-stabiliser (D:S) ratio on particle size. ***Data set presented was mathematically processed with double logarithmic and Box-Cox transformations. **(E)** Pareto chart of the standardised effects and modelling statistical parameters. **(F–J) Triamcinolone acetonide (TA): (F)** Effect of stabiliser type on mean particle size at 1 wt%. ****All the stabilisers showed statistically significant difference, except P407 and TPGS. ; **(G–I)** response surface plots illustrating the effects of bead volume, agitation speed, and D:S ratio on particle size; **(J)** Pareto chart of the standardised effects and modelling statistical parameters. Response surface models identify the key process parameters influencing particle size for each drug.

NCs CHARACTERIZATION RESULTS

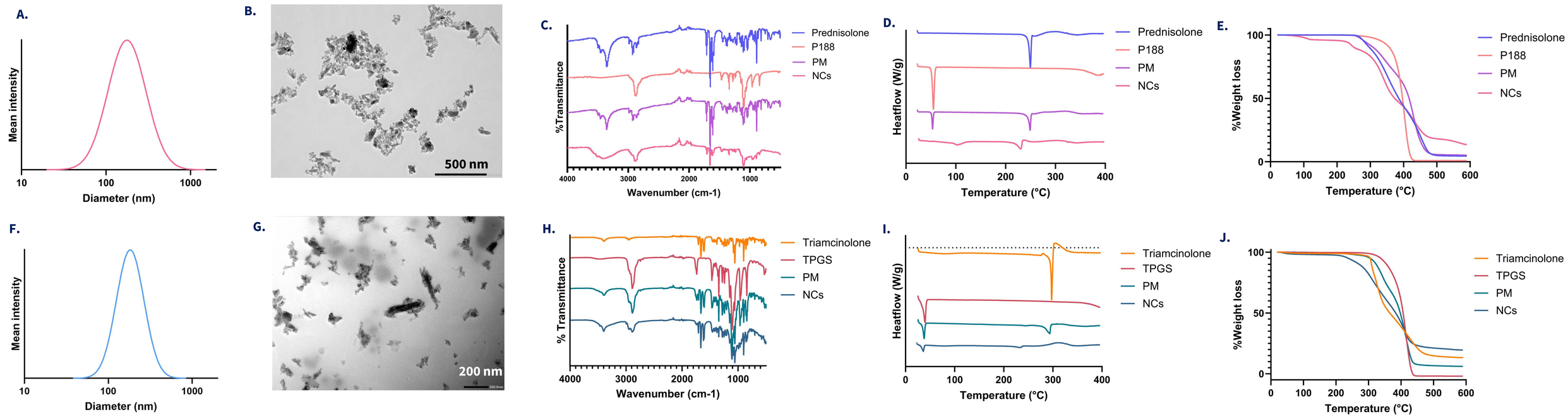


Figure 2. Physicochemical characterization of drug nanocrystals (NCs). **(A–E)** Characterization of **prednisolone NCs**: **(A**) particle size distribution measured by dynamic light scattering (DLS); **(B)** transmission electron microscopy (TEM) image showing particle morphology; (**C)** Fourier-transform infrared (FTIR) spectra of prednisolone, P188, PM (physical mixture), and prednisolone NCs; **(D)** differential scanning calorimetry **(DSC)** thermograms of prednisolone, P188, PM, and prednisolone-loaded NCs; and **(E)** thermogravimetric analysis (TGA) profiles of prednisolone, P188, PM, and prednisolone-loaded NCs. **(F–J)** Characterization of **triamcinolone-loaded NCs**: (F) DLS particle size distribution; (G) TEM image; (H) FTIR spectra of triamcinolone, TPGS, PM, and triamcinolone-loaded NCs; (I) DSC thermograms of triamcinolone, TPGS, PM, and triamcinolone-loaded NCs; and (J) TGA profiles of triamcinolone, TPGS, PM, and triamcinolone-loaded NCs.

CONCLUSIONS AND FUTURE WORK

1. A **predictive** statistical model was obtained to consistently produced optimized prednisolone and triamcinolone acetonide NCs.
2. The optimized NCs formulations showed acceptable physical and chemical **stability** and will be incorporated in a **nanofibre patch for ophthalmic drug delivery**.

REFERENCES

1. C.E. Egwuagu, L. Sun, S.-H. Kim, I.M. Dambuza. Current Molecular Medicine. 2015. 517 – 528
2. F. A. Maulvi, K. H. Shetty, D. T. Desai, D. O. Shah, M. D.P. Willcox. International Journal of Pharmaceutics. 2021. 121105
3. J. Li, Z. Wang, H. Zhang, J. Gao, & A. Zheng. Drug Delivery. 2021. 19–36.