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Application of Design of Experiment for development of orally disintegrating tablets

Irina Ermolina[a]*, Ellen Hackl[b]

[a] Leicester School of pharmacy, De Montfort University, The Gateway, Leicester, LE1 9BH, UK

[b] Reading School of Pharmacy, University of Reading, Reading, RG6 6DX, UK

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*Corresponding author.
Tel.: +44 116 257 7870
E-mail: iermolina@dmu.ac.uk

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SUMMARY

The current work presents the formulation development methodology for Orally Disintegrating Tablets (ODTs) using Design of Experiment (DoE). The statistical software JMP was used to design the experiments and analyse the data for producing sodium Ibuprofen freeze-dried ODTs. In the first stage, several pure excipients (polymers, amino acids, and polyols) were freeze-dried and the quality attributes of the cakes were evaluated. Four critical quality attributes (CQAs) were determined based on the target profile: disintegration time, mechanical strength, moisture uptake, appearance. In the second stage, the placebo tablets comprising sodium alginate, alanine, and mannitol (working as a matrix shape-former and lyo-/cryo-protectors), were designed using Mixture DoE, freeze-dried and characterized to identify the optimal combination of the excipients. In the third stage, the ODTs containing sodium Ibuprofen were designed within a reduced design space to optimize the formulation. The wettability and dissolution of the ODTs were studied. The proposed methodology enabled the estimation of working design space and facilitated the production of freeze-dried ODTs with the required quality attributes. Sodium alginate was identified as the key excipient in the formulation, affecting all CQAs. The optimal combination of sodium alginate, alanine and mannitol corresponding to the desirable target profile was found (30%:40%:30%).

INTRODUCTION

Tablets are the most popular, patient-friendly, and cost-effective dosage forms for oral administration. However, they have certain limitations when used in pediatric or geriatric patients due to difficulties in swallowing or discomfort. Orally Disintegrating Tablets (ODTs) meet both medical and patient requirements, as they swiftly disintegrate in the mouth without the need for water, making them easy to swallow and allowing for partial absorption within the oral cavity. The manufacturing process for ODTs often involves freeze-drying, which imparts the tablets with their characteristic porous structure facilitating rapid liquid absorption and quick disintegration upon contact with saliva.

The formulation development of ODTs can be challenging as they tend to be fragile and require specific excipients (matrix formers) to enhance their mechanical strength. Additionally, cryo- and lyo-protectors are used to ensure the tablets' stability and integrity. In this work, we demonstrate the application of statistical JMP software in formulation development to design the experiments (Mixture DoE) and analyse data to produce sodium Ibuprofen (Na Ibu) freeze-dried ODTs.

The study comprised 3 stages: (1) a preliminary screening of the properties of the pure excipients; (2)

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the manufacturing of placebo tablets using selected polymers, amino acids, and polyols; (3) the manufacturing of Na Ibu orally disintegrating tablets based on the optimized Design Space obtained from the placebo tablets.

MATERIALS AND METHODS

The 5% and 10% aqueous solutions of several pure excipients (polymers, amino acids, disaccharides, and polyols) were prepared. For stage 2, the 10% stock solutions of sodium alginate (Na Alg), alanine and mannitol were combined in various proportions according to Latex Mixture design (1st DoE). For stage 3, the 10% stock solutions of excipients were prepared on the base of 2% sodium Ibuprofen in a smaller design space (using 2nd DoE). All samples were lyophilised using a Vitris (Biopharma) freeze-drier. Freeze-dried products (cakes in vials or tablets in blister packs) were characterized using visual observation, Texture Analysis (TA.XT Plus) [1], TGA, disintegration, and gravimetric moisture uptake (at 75%RH) tests.

RESULTS AND DISCUSSION

The critical quality attributes (CQAs) of ODTs were determined based on the target profile and included disintegration time (within 60 seconds); mechanical strength (penetration force > 1.5 kg); moisture uptake (less than 15% at 75% RH); and good appearance (with no cracks and shrinkage).

In the first stage, several polymers (both natural and synthetic), amino acids, disaccharides, and the polyol mannitol were freeze-dried, and the quality attributes of the freeze-dried cakes were evaluated. From these, three excipients (Na Alg, alanine, and mannitol) were selected to formulate placebo ODTs in vials (Fig. 1) using mixture DoE (Fig. 2). The statistical analysis carried out using JMP software resulted in a model comprising three main effects and 2-way interactions, effectively describing the product quality attributes and identifying the critical material attributes. Na Alg exhibited statistically significant effect on all 4 CQAs, while the alginate & mannitol interaction was found to be crucial for disintegration and appearance only.

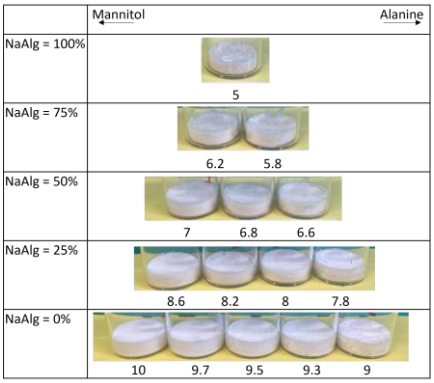

Fig. 1. *The freeze-dried placebo tablets. Numbers correspond to appearance, from 1 (worst) to 10 (best).*

The contour profile (Fig 2, left) demonstrated that all four responses are affected by Na Alg, and an optimal design space (red triangle, DoE 2) can be selected to formulate Na Ibu tablets with desirable properties (Fig 2, right).

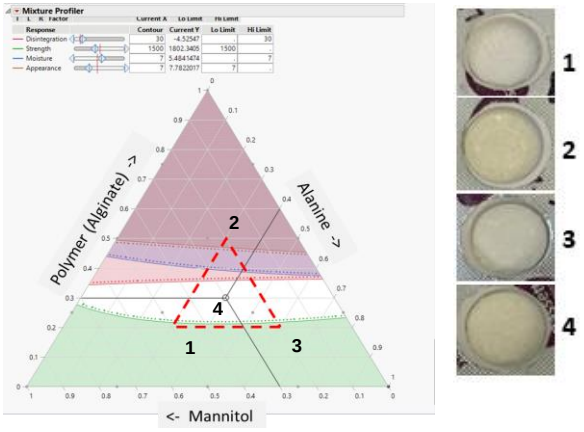

Fig. 2. *(left) Contour profile (mixture DoE) for placebo tablets (stage 2); (right) ODTs in blister pack (stage 3).*

CONCLUSIONS

The proposed methodology (using DoE) enabled the successful estimation of a working design space and facilitated the production of freeze-dried ODTs with the required quality attributes. The optimal combination of excipients, NaAlg:Ala:Man, was found to be approximately 30%:40%:30%.

REFERENCES

[1] Hackl, E.V. and Ermolina, I., 2016. Using Texture Analysis technique to assess the freeze-dried cakes in vials. J. of Pharm. Sci. 105, 2073-2085.