Reconstitution Time for High Concentrated Lyophilized Proteins: Role of Formulation and Protein

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PURPOSE

The factors influencing reconstitution time of highly concentrated proteins in lyophilized formulations are yet to be fully elucidated and are the focus of the present work.

METHODS

Ten formulations differing in their excipient composition and/or protein were lyophilized using a conservative cycle. Lyophilized cakes were characterized for reconstitution time, cake wettability, liquid penetration into cakes, cake disintegration and porous structure using methods developed in the lab. Formulations were reconstituted in two ways for viscosity measurement: (i) Using the full volume of the reconstitution fluid (referred to as ‘full recon’) and (ii) Using 1/3rd of the reconstitution volume (referred to as ‘1/3rd recon’). Reconstitution using 1/3rd volume was explored for its ability to mimic the high viscosity expected near the surface of the dissolving cake during reconstitution.

RESULTS

Reconstitution time was found to depend on the protein to sugar ratio and the specific protein in the formulation. Formulations with lower protein to sugar ratio were characterized by lower contact angle (better wettability), faster penetration of the reconstitution fluid to the cake interior, easier cake dispersion and larger average pore diameter, all promoting faster reconstitution. However, for formulations with higher protein to sugar ratio, none of these cake properties correlated with reconstitution time. Interestingly, while the viscosities of these formulations were within 7 cP at full recon, viscosities at 1/3rd recon (ranging from 7-500 cP) were significantly different and, more importantly, they correlated reasonably well with the reconstitution time. When a linear model was fitted to the data, the reconstitution time of the formulations correlated directly with viscosity at 1/3rd recon ($R^2 = 0.94$).

CONCLUSIONS

Low protein to sugar ratio improved cake wettability. Larger pores improved accessibility of the reconstitution fluid to the cake interior thereby promoting reconstitution. Lower viscosity during dissolution of the cake (indicated by viscosity at 1/3rd recon) promoted faster reconstitution by potentially enabling higher convective flow of the bulk fluid near the surface of the dissolving cake. Viscosity of a concentrated solution (e.g., viscosity at 1/3rd recon) provided a better understanding of the reconstitution behavior than viscosity of the final reconstituted solution.

REFERENCES