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Lyophilised mannitol: an attractive solid dosage from excipient

Mannitol is a pharmaceutical excipient that is receiving increased popularity in solid dosage forms. This study contributes to the development of mannitol as a potential excipient of the first choice. The purpose was to address the theory that the physicochemical, mechanical, and pharmaceutical properties of lyophilised mannitol (LM) powders are strongly dependent on the concentration of mannitol solution subjected to lyophilisation as one variable. Mannitol was lyophilised from a series of aqueous solutions (from 1% to 15%, *w*/*v*) using an identical protocol. LM powders were then characterized in terms of physicochemical and mechanical properties. In vitro dissolution profiles of a model poorly soluble drug, indomethacin, from LM tablets were evaluated. The results showed that LM powders are solids occupying approximately the volume of the former solution. Fluffy LM powders were obtained with yields above 99% (w/w). Therefore, the physicochemical, mechanical and pharmaceutical properties of LM are strong functions of mannitol concentration. By decreasing mannitol concentration, the true density, bulk density, cohesivity, flowability, netcharge-to-mass ratio, and relative degree of crystallinity of LM were decreased, whereas the breakability, size distribution, and size homogeneity of LM particles were increased. The mechanical properties of LM tablets improved with decreasing mannitol concentration (tensile strength of tablets were 5.7, 3.1, 0.8 and 0.4 MPa for mannitol lyophilised from 1%, 5%, 10% and 15% respectively). The use of LM has profoundly improved the dissolution rate of indomethacin from tablets in comparison to commercial mannitol (dissolution efficiency, 62.7% to 87.5% versus 25.1%). This improvement exhibited an increasing trend with decreasing mannitol concentration.

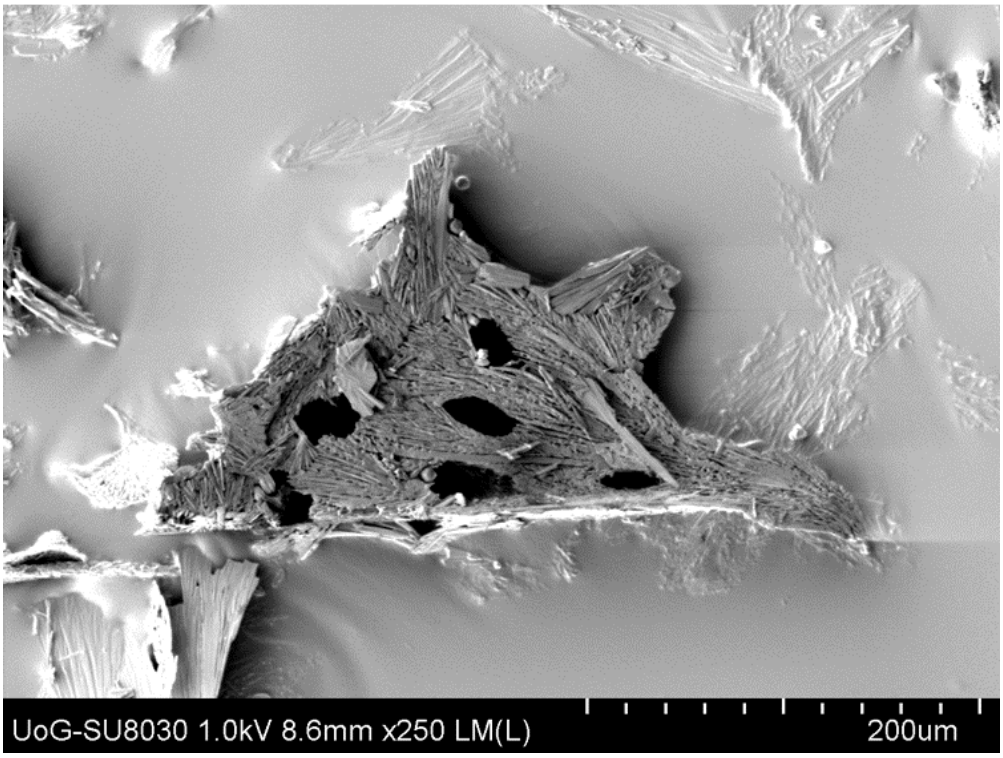

Fig. 1. Scanning electron microscopy (x 250) of mannitol lyophilised from 1% (w/v) aqueous solution.

LMs revealed fractured particles with wrinkled (corrugated) surfaces, producing open (rather than packed) particle structures (Fig. 1 and 2). Microstructural observations with scanning electron microscopy showed mannitol particles lyophilised from concentrations ≤5% (*w*/*v*) to have macroporous surface texture characteristics composed of a microstructured network of particles with visible large pores and cavities (Fig. 1 and 2). This is because lyophilisation process allows the ice to sublime, leaving voids within the structure without major shrinkage. Mannitols lyophilised from lower concentrations were more desirable in tableting than mannitols from higher concentrations due to their better mechanical and dissolution properties. The micro- and macro-structural changes of mannitol products lyophilised from solutions having different concentrations can be predicted. By decreasing mannitol concentration, the density, flowability and crystallinity of lyophilised mannitol (LM) were decreased, whereas the porosity and breakability (fragility) of LM were increased. Clear trends of improved mechanical properties and enhanced dissolution rates were established with decreasing the concentration of mannitol solution subjected to freeze-drying. The formulators could therefore optimize the mechanical and dissolution properties of LM tablets via the careful selection of mannitol concentration prior to freeze-drying.

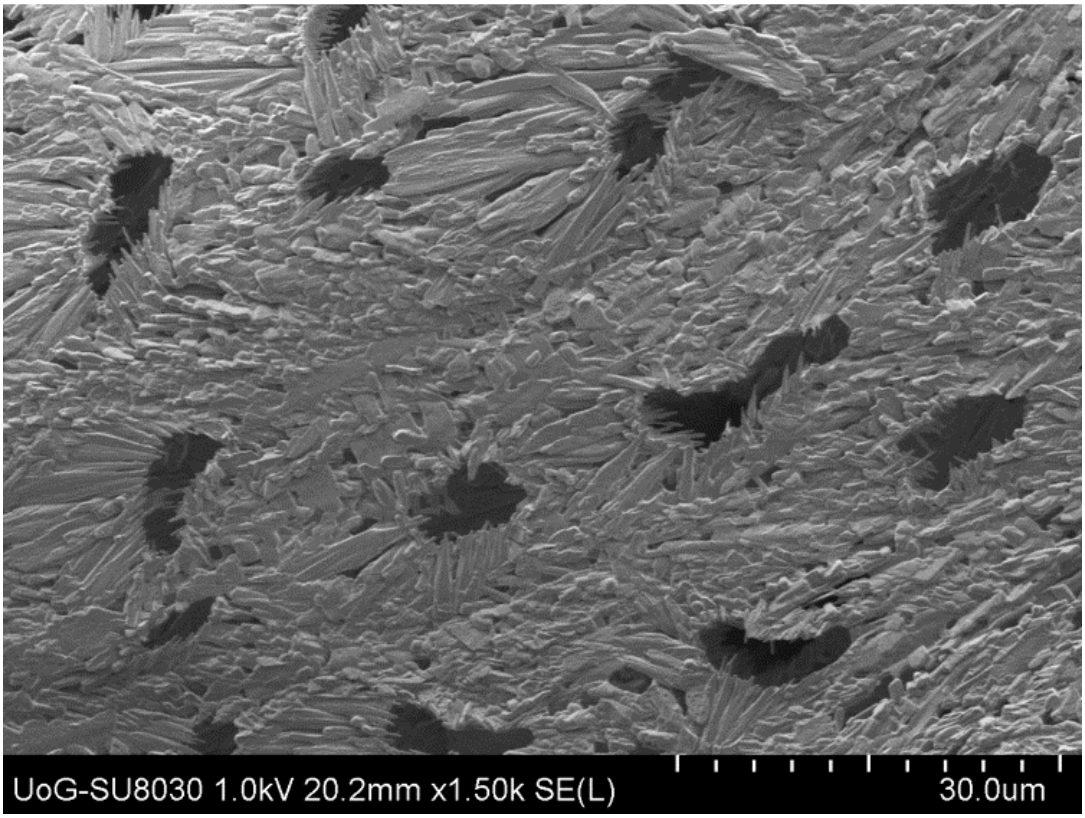

Fig. 2. Scanning electron microscopy (x 1500) of mannitol lyophilised from 1% (w/v) aqueous solution.

This work recommends the use of mannitol lyophilised from 1% (*w*/*w*) mannitol for the preparation of directly compressible preparation with excellent mechanical and rapid dissolution properties. Mannitol particles lyophilised from the lowest concentration (1%, *w*/*v*) were ultra-fluffy (bulk density of only 0.03 g/cm^3), porous, flake-shaped, and produced the best tablets with ×9.1 fold increase in tensile strength (5.04

MPa versus 0.56 MPa) and ×3.5 fold increase of dissolution efficiency (87.5% versus 25.1%) of indomethacin in comparison to CM. Further optimisation of the utilization of lyophilisation in the design of mannitol particles with desired pharmaceutical properties should be considered.

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