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RESEARCH ARTICLE

WATER AND TEMPERATURE INDUCED POLYMORPHIC TRANSFORMATIONS OF MANNITOL

[1.2]Dilip. M. Raut*, [1]D. T. Mahajan, [1]D. M. Sakharkar, [1]P. S. Bodke, K.V.Pavan, Ravikiran Allada, Girish Deshpande, Durvas Patil and Avinash Patil

[1]Department of Chemistry, Vidya Bharti Mahavidyalaya, C. K. Naidu Marg, Camp Amravati (Maharashtra) INDIA
[2]Mylan Laboratories Limited R&D, Bollaram, Hyderabad, AP, INDIA

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ABSTRACT

The effects of water and temperature on the polymorphic transition of crystalline mannitol were investigated. Mannitol has different polymorphic forms, and was classified as alpha, beta, and delta form, respectively, by Walter-Le´vy (C.R. Acad. Sc. Paris Ser. C (1968) 267, 1779). The behavior of representative crystalline form was studied using water granulation and temperature induced mechanism. The different powder X-ray diffraction patterns obtained before and after water granulation confirmed that water induced polymorphic transition had occurred. Morphological changes were observed with increase in the specific surface area of the sample from 1.044 to 1.206m2/g, It was also found that decrease the particle size upon water granulation. At the same time temperature induced polymorphic transformation observed using Differential Scanning Calorimetry (DSC), were reported glass transition temperature of Mannitol is determined from inferences. The glass transition temperature denotes the stability of amorphous Mannitol, which is necessary to be stored only below this grass transition temperature else it may easily re-crystallize in to a thermodynamically stable crystalline form. When considering the mechanism of these polymorphic transitions, the results from PXRD, DSC, TGA, BET SSA, PSD and Sorption analysis indicates that water granulation process leads to the polymorphic transformation and increases the specific surface area with decrease in particle size initially, but later it gets agglomerated over a period of time resulting increase in particle size . Where as temperature induces polymorphic transformation from crystalline to amorphous, which needs to be stored below its glass transition temperature.

INTRODUCTION

Mannitol, a naturally occurring hexa-hydric alcohol, is commonly used as a pharmaceutical excipient for tablets due to excellent safety and compatibility with drugs (Kibbe, 2000). Mannitol is a particularly useful excipient when used with moisture sensitive drugs because of its non-hygroscopicity which has been proved in this article using sorption analysis. Mannitol generally occurs as a crystalline excipient and several polymorphic forms are known to exist. Wet granulation, the process of adding a liquid solution to powders, is one of the most common ways to granulate. The process can be very simple or very complex depending on the characteristics of the powders. During the manufacturing process there are chances to generate the new polymorphic forms of both active pharmaceutical or inactive ingredients due to wet granulation and these surprises leads to the misinterpretation of the physical property data. Mannitol is one of the potential inactive ingredients used as a diluent or bulk excipient in the formulation. The anhydrous polymorphic form of Mannitol can be converted into another form during the wet granulation which shows different Powder X-Ray diffraction pattern, low particle size and high specific surface area using BET. At the same time crystallization of many organic materials can result from the transformation of an amorphous material form as it moves through the glass transition conditions. The glass transition denotes an increase in molecular mobility and hence a decrease in mechanical strength of the compound [1]. The glass transition temperatures of organic materials are affected by heating rate [2] as well as the level of chemical plasticizers present such as moisture [1] and other additives [3].

Differential Scanning Calorimetry (DSC) has been widely used to understand the effect of changes in temperature on glass transition and crystallization of many organic materials including excipients. Crystallization of amorphous excipients can be induced by the environmental conditions they are exposed to during manufacture, transport, storage and processing; specifically temperature and relative humidity. Our current study contributes to the development of Mannitol potentially as the excipient of first choice by further understanding its behavior under common environmental conditions. The reported glass transition temperature of Mannitol is determined either from DSC using experiments. The glass transition temperature denotes the stability of

Corresponding author: dilip.raut@mylan.in

amorphous Mannitol, which is necessary to be stored only below this grass transition temperature else it may easily re-crystallize in to a thermodynamically stable crystalline form.
In this study, we report preliminary data on the effect of water granulation and temperature on the glass transition behavior, denoting water induced crystallization of Mannitol and temperature induced re-crystallization at selected temperatures.

MATERIALS AND METHODS

Mannitol SD200 is the PERLITOL 200SD was sourced from ROQUETTE Pharmaceuticals, commercial supplier and used as received. The water granulated material was prepared using solvent drop grinding method by addition of water drop wise in mannitol powder sample and ground using mortar and pestle. The water granulated material then dried at 50°C for 60minuts.

Analytical Methodology

Thermal Analysis

Simultaneous Thermogravimetry (TGA) and Differential Scanning Calorimetry (DSC) analysis thermogram were generated using a METTLER TOLEDO. Approximately 5 mg sample were scanned under a dry nitrogen purge from 0 to 250°C at 10°C/min and analyzed using DSC. Where as approximately 10 mg sample were scanned under a dry nitrogen purge from 25 to 250°C at 10°C/min and analyzed using TGA.

Powder X-Ray Diffraction (XRD)

X-ray powder diffraction was performed on the samples using the Bruker D8 advance X-ray diffractometer. The instrument was equipped with a 2.2 kW Cu anode X-ray tube, high temperature stage, and high-speed position sensitive detector (PSD). Cu Ka radiation (Wavelength = 1.5418A °) was used to obtain all powder diffraction patterns. A nickel filter was placed in the receiving path of the X-rays to remove the Kb radiation. Mannitol material was mounted and analyzed on a front loading sample holder, without any special sample preparation. All scans were performed over the range of 3–45° 2 theta, at a 0.01 step size for 0.1 s/step.

Particle Size Distribution (PSD)

Particle size distribution of the Mannitol and water granulated Mannitol were determined using laser diffraction technique. Malvern Mastersizer 2000 instrument were used and analysis were performed using dry method. Approximately 1gm of each sample was transferred in dried and clean sample feeder tray, vibration feed rate 50% and dispersive air pressure 2 bar were applied and measured the particle size.

BET specific surface area analysis

Specific surface area of Mannitol and water granulated mannitol sample were measured by using QuadraSorb SI BET automated surface area and pore size analyzer. Analysis was performed using nitrogen gas as an adsorbate with multi-point model.

Sorption Analysis

Sorption analyses were performed using IGAsorp Moisture Sorption Analyser from HIDEN ISOCHEMA, analysis experiments are performed by stepping the humidity (% RH) over a broad range at constant temperature.

RESULTS AND DISCUSSION

Thermal Analysis

Comparing as such Mannitol with water granulated Mannitol via thermal analysis clearly illustrates that there is no change in as a heating result, indicates that after water granulation, the generated polymorphic form is anhydrous. Where as, as such mannitol after melting cooled to 0°C and reheated till to melt shows glass transition and recrystallization events. Representative thermograms are provided below in Figure 1.

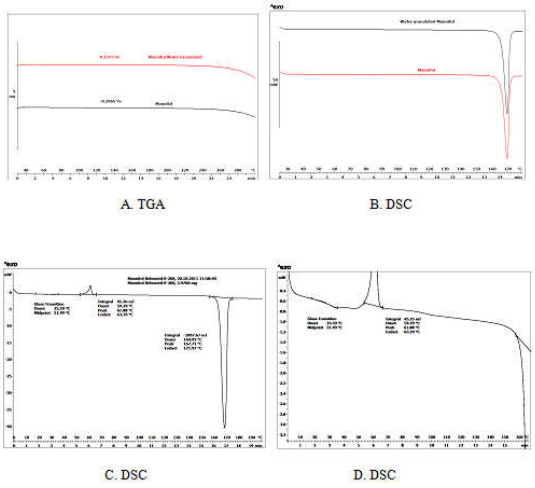

Figure 1. A: Comparison of TGA curves for as such and water granulated Mannitol sample
B: Comparison of DSC curves for as such and water granulated Mannitol sample
C: DSC Curve of Mannitol shows recrystallization and glass transition events
D: Zoom DSC Curve of Mannitol shows glass transition events

X-Ray Diffraction

X-ray powder diffraction clearly discriminates between the as such Mannitol and water granulated form of Mannitol as shown in Figure 2. Upon the water drop grinding water granulation, the lattice undergoes a transition. This transition results in the formation of a new lattice configuration, which is distinct from commercially available Mannitol.

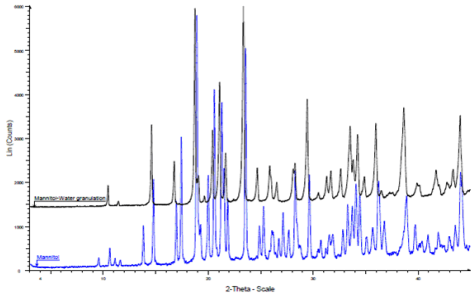

Figure 2. Overlaid powder x-ray diffraction pattern of as such Mannitol correlated with water granulated Mannitol.

Particle Size Distribution (PSD)

Comparison of as such Mannitol to the same lot of material after water granulation illustrates the impact of grinding and drying during granulation upon the particle size shown in table-1. The same granulated material was packed in HDPE bottle for three days at room temperature (25°C) and room relative humidity (50%RH) and again analyzed using the particle size distribution and hard lumps has been observed.

Table 1. PSD Results for as such Mannitol, after water ranulation and the granulated material kept in HDPE bottle for 3 days.

S. No.	Sample	PSD		
		D10	D50	D90
01.	Mannitol	28.187	117.312	205.081
02.	Water granulated Mannitol	0.481	1.763	4.611
03.	Water granulated Mannitol, HDPE , 3days	0.844	64.349	400.144

BET specific surface area analysis

Decrease in the particle size increases the specific surface area, and at the same time granulation and drying leads to increase the porosity. Surface area of as such Mannitol and water granulated Mannitol sample were measured using QuadraSorb SI BET automated surface area and pore size analyzer. Results are reported in below graphs and table-2

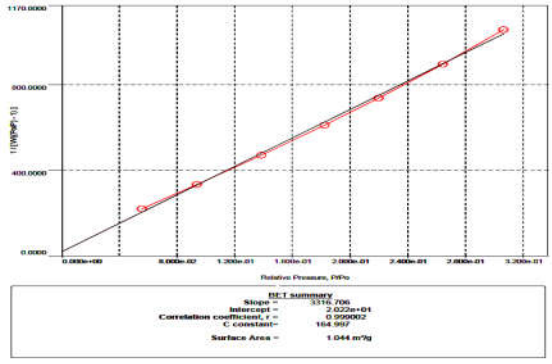

Figure 3A. Multi-point model for as such Mannitol

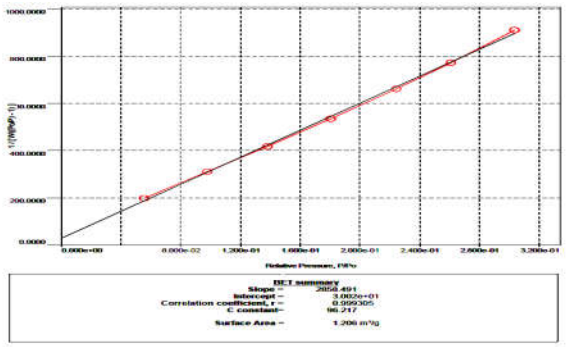

Figure 3B.Multi-point model for water granulated Mannitol using water drop grinding method

Sorption Analysis

Sorption analyses were performed using IGAsorp Moisture Sorption Analyser using nitrogen as a carrier gas to generate the humidity, analysis experiments are performed by stepping the humidity (% RH) over a broad range at constant temperature. All studies were performed at about 30°C. In turn each sample was loaded into the IGAsorp under atmospheric conditions and the initial weight measured. Sample sizes varied between 30 and 70mg. The environment around the sample was then set to 50%RH and the sample was allowed to equilibrate. A moisture adsorption isotherm was performed on each sample which consisted of step like changes in RH between 60%RH and 90%RH for adsorption. At each set-point the equilibrium mass and kinetic rates constant were determined using the IGA Method. Based on the results it has been observed that As such Mannitol as well as Mannitol after water granulations both are not hygroscopic and total mass up to 90% RH increased by less than 1.0%.

Table 2. BET Specific surface area results for as such Mannitol and water granulated Mannitol

S. No.	Sample	BET Surface area
01.	As such Mannitol	1.044 m2/g
02.	Water granulated Mannitol	1.206 m2/g

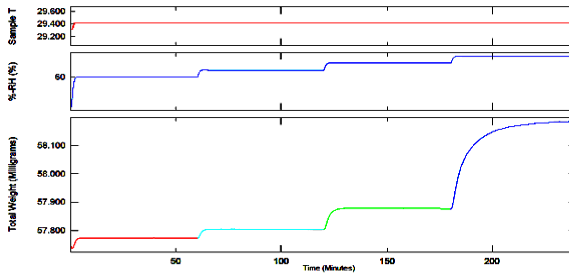

Figure 4A, Mannitol moisture sorption isotherms

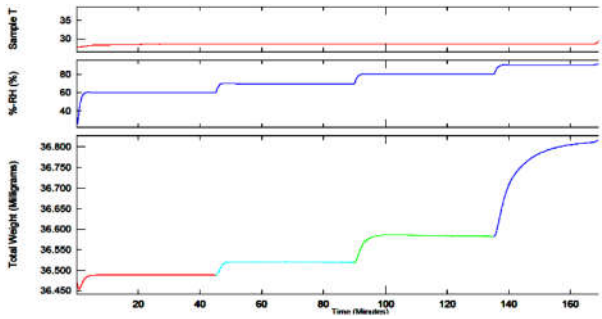

Figure 4B. Water granulated Mannitol moisture sorption isotherms

CONCLUSION

Water granulation can create new crystal form which does not revert back to the original form at room RT and room RH. Evidence for creation of this new phase includes a unique X-ray diffraction pattern. Adjustment of the lattice affects the mechanical strength of the water granulated crystal form which readily fractures producing crystals with smaller particle size due to water drop grinding method. This reduction in particle size is evident from particle size data. Understanding this physical consequence of drying displays the importance of complete characterization of an excipient under various environmental conditions of water granulation and temperature. Without the knowledge that this signature

indicates granulation, the result may be interpreted as identification of an undesirable form of active pharmaceutical ingredient rather than evidence that the desired form was converted. Likewise, without a complete understanding of this granulation phenomenon, it is may be possible to obtain flawed results during routine analysis if care is not taken to control the exposure of the excipient form to environmental or testing conditions that promote granulations. In conclusion, granulation of pharmaceutically accepted excipient can easily lead the polymorphic transformation. At the same time temperature induced polymorphic transformation observed using DSC, were reported glass transition temperature of Mannitol is determined from inferences. The glass transition temperature denotes the stability of amorphous Mannitol below which it is necessary to store or else it can be easily re-crystallize and converts to thermodynamically most stable polymorphic form.

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