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**Original Article**

# Effects of water content, particle size and density on the dissolution profile of mannitol

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## ABSTRACT

In this study the reason for fluctuation of assay test results during in process quality control of injectable mannitol solution production was investigated. Particle size distribution, water content, thermographic behavior, Fourier-transform infrared spectroscopy (FTIR) and dissolution profile were evaluated using differential light scattering, Loss on drying method, differential scanning calorimetry (DSC), FTIR and intrinsic dissolution rate respectively. Results showed that change in water content of mannitol powder could result in particle size distribution and dissolution profile change. Based on the results of this study, we recommend that water content of mannitol must be measured before adding it to the any formulation. Manufacturers could be able to justify mixing time, temperature and rate based on water content test results. It will be helpful for pharmaceutical industries if mannitol producers add some extra tests to their current Certificate of Analysis (CoA) including particle size distribution, polymorphism, and dissolution profile based on intrinsic dissolution rate (IDR) which are not pharmacopoeia tests for this material.

**Key words:** mannitol, dissolution profile, IDR, water content, in process control

## INTRODUCTION

Mannitol is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odorless, crystalline powder, or free flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism [1,2]. Mannitol widely used in pharmaceutical industries as excipient and active pharmaceutical ingredient [3].

In Pharmaceutical industry, any mannitol solution is tested for assay during production of the solution

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by in process control team. Some days, the results in our plant, were not consistent and showed fluctuations when sampling was done in pre-defined time intervals from different levels of production vessel during in process controls although final solution shows normal assay test. It seems just solution behavior changed not total dissolution range. As this was not routine observation, investigations were started by researchers to find relation between changes in dissolution behavior of mannitol and material characteristics.

In this study, four batches of raw material were selected to investigate. From these batches, two of them were used in the production of product with assay results fluctuations.

FTIR, Microscopic imaging, particle size analysis, moisture content detection and calorimetry analysis as well as intrinsic dissolution rate studies were designed for all four randomly selected raw material batches.

Our findings showed that, the water content of mannitol plays crucial role in particle size distribution and intrinsic dissolution rate (IDR) profile. The results of this study proves that considering the water content, particle size distribution and IDR of mannitol, can help us to make better decision about mixing time and sampling point for in process control.

## MATERIALS AND METHODS

**Materials:** Mannitol powder and water for injection (WFI).

**Methods:**

*Water content measurement:* This was done using LOD (Loss on Drying) method based on the mannitol monograph (USP 41).

*Bulk density determination:* For all four samples density was determined to confirm other investigations as well as to achieve a simple and cheap control to let us get sense about material condition before usage.

*FTIR:* FTIR patterns of mannitol samples were investigated using Agilent instrument.

*Particle size analysis:* Particle size analysis was carried out using Malvern Zetasizer ZS (Malvern Co., UK).

*Differential Scanning calorimetry:* DSC Thermography analysis was done using DSC 60 Schimadzu equipment in temperature range between 10-240 °C under constant heating rate of 10 °C/min.

*IDR:* IDR tests were carried out based on USP 41 General chapter 1087 (USP 41 NF 36), using Erweka 820 T system at room temperature [3]. Water for Injection (WFI) 900 ml was selected as dissolution medium. Mannitol samples were compressed at 3000-3500 psi to make tablets with 8 mm diameter.

## RESULTS AND DISCUSSIONS

Samples were coded using Latin numbers 1-4. Samples 1 and 2 were the ones with probable problem or character changes.

*FTIR Peaks:* In 3300-3800 area peaks were appeared for samples 1 and 2 which could present water existence.

*Particle size analysis:* Although most of particles in all batches were in size range between 0.9 - 1.096 µm, results showed some differences in d (10), d (50) and d (90) of studied batches as well as specific surface area of them.

Table 1 shows the d (10-50 and 90) of the mentioned samples. A significant particle size enlargement was detected in one of the samples with assay problem in the related solution. The particle size enlargement in sample number 2 was confirmed by microscopic pictures as presented below.

**Table 1**. Results of size distribution studies

| Sample Number | d(10) µm | d(50) µm | d(90) µm | Specific surface area $m^2/g$ | Uniformity |
|---|---|---|---|---|---|
| **1** | 0.842 | 1.108 | 2.085 | 0.334 | 0.517 |
| **2** | 1.320 | 1.917 | **5.112** | 0.24 | **0.705** |
| **3** | 0.841 | 1.105 | 2.100 | 0.35 | 0.528 |
| **4** | 0.959 | 1.213 | 2.359 | 0.288 | 0.535 |

Figure 1a-b presented results of size and shape investigations of samples 2 and 3.

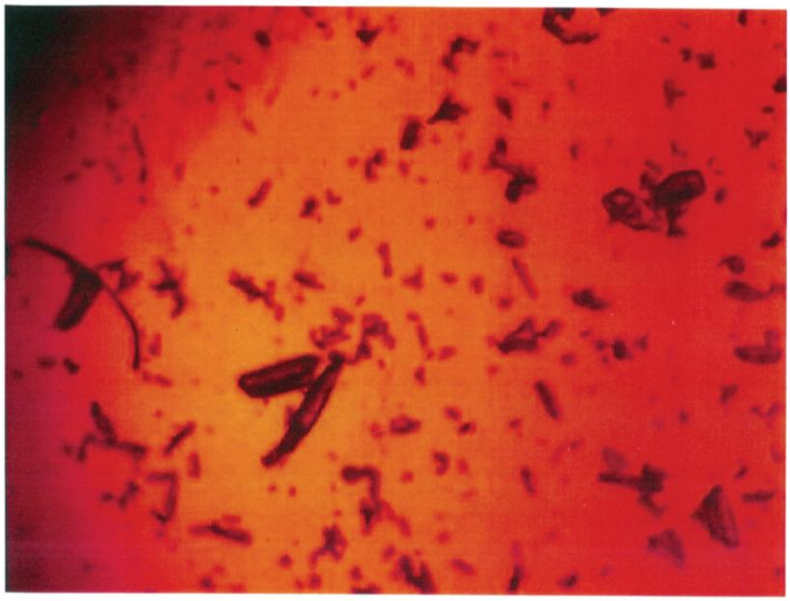

**FIGURE 1a:** microscopic photo of sample 2.

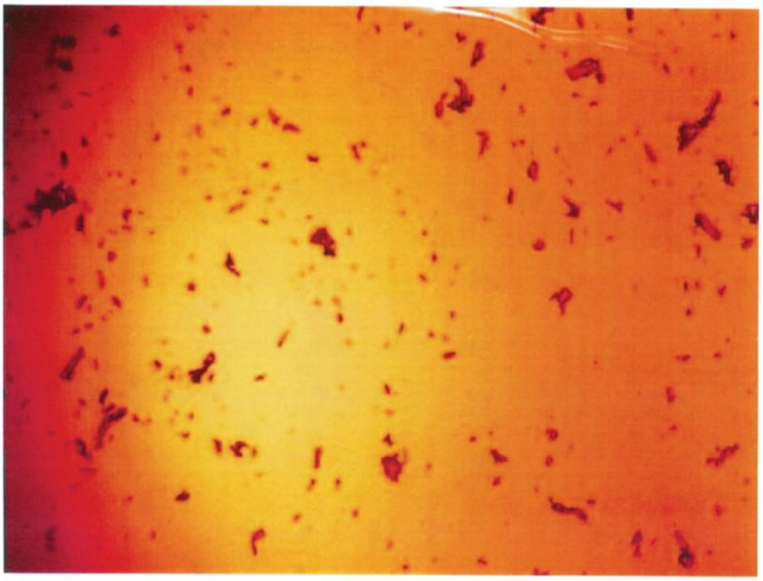

**FIGURE 1b:** microscopic photo of sample 3.

*Investigation of LOD and bulk density:* LOD measurement was done for all the samples. The values were compared with the LOD of samples which were claimed in their CoA (Certificate of Analysis) at the zero time (when samples received from supplier). Table 2 show the results of LOD and density for the samples. Results demonstrated that in batch No.1 significant water absorption happened. In batch No.2 moderate level of absorption was seen. Differences in bulk density is in parallel with the water content results. Other studies recommended bulk density measurement as a factor in powder changes [4].

*DSC:* Figure 2a-b show the DSC graphs for samples 1-3. Probability of water absorbance in sample 2 was seen in DSC thermograms with observation of additional peak in region between 30-40 °C.

*IDR:* Figure 3 shows dissolution profile for all four samples. Results show that sample No. 1 continues to release for more than 140 minutes, and sample No.2 after 180 minutes dissolution profile is going to rise, however samples 3 and 4 show regular dissolution profile in that most of the compressed mannitol was dissolved within 40 minutes. Upon checking dissolution vessels, remaining of undissolved mannitol disks for samples 1, 2 and 4 was detectable.

**Table 2.** Results of LOD and density determination for the samples

| **Sample number** | **LOD** (at using time) | **LOD** (zero time) | **Bulk Density** (g/ml) |
|---|---|---|---|
| 1 | 0.11 | 0.05 | 0.714 |
| 2 | 0.16 | 0.13 | 0.714 |
| 3 | 0.09 | 0.13 | 0.571 |
| 4 | 0.06 | 0.04 | 0.667 |

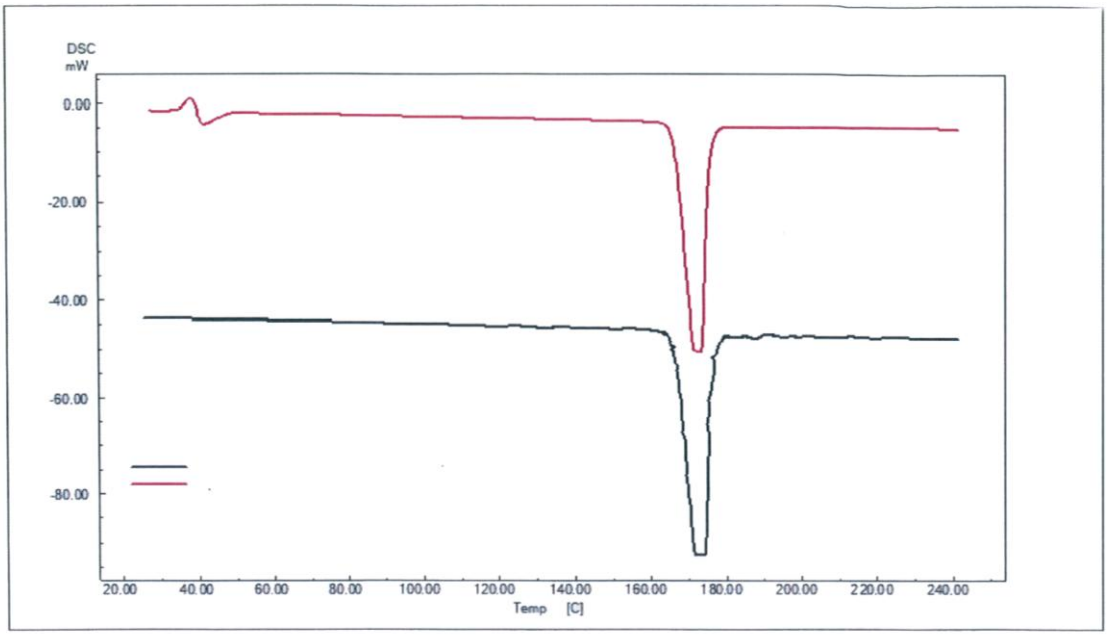


**FIGURE 2a**: DSC results for sample 1 (black) and 2 (red).

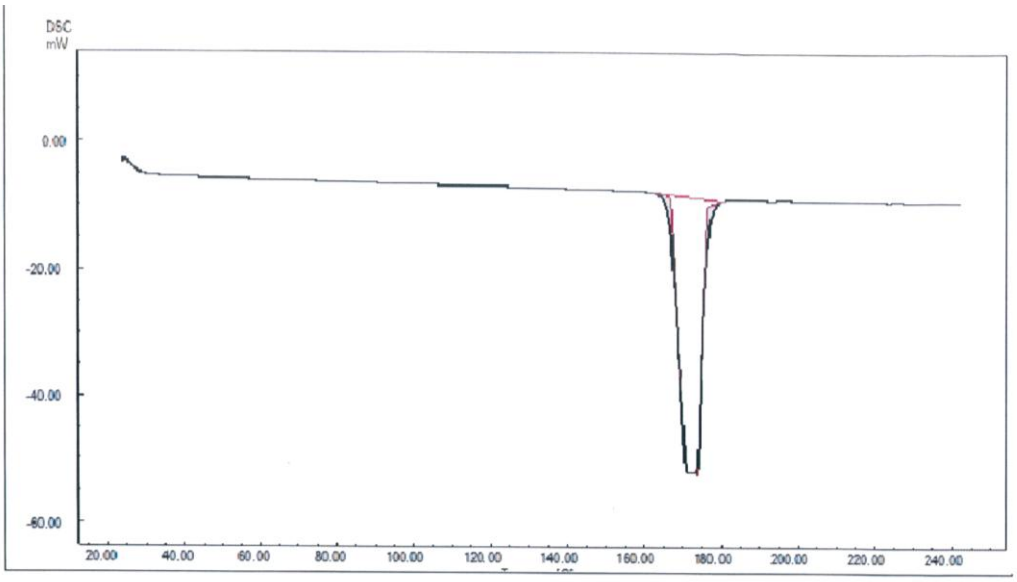


**FIGURE 2b**: DSC result for sample 3.

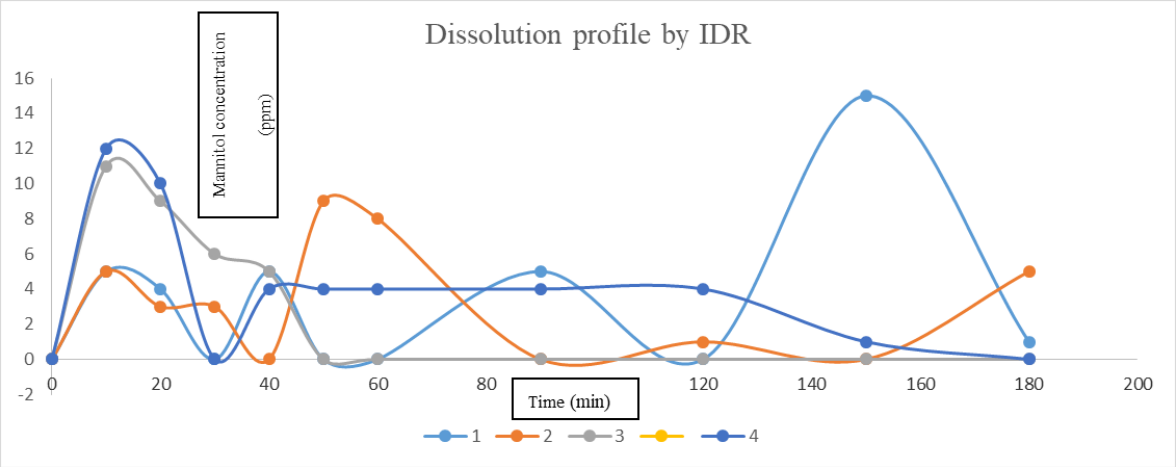


**FIGURE 3.** Dissolution profile of samples 1-4 by IDR.

## DISCUSSION

It seems that changing in water content and particle size distribution of mannitol powder could affect the dissolution rate of the powder significantly. The effect of humidity on powder behavior was studied before and scientists demonstrated that powder properties can change significantly when a material is exposed to different humidity. These behaviors could not be predicted from first principles. They found that the relationship between humidity and powder behavior is complicated. Therefore, comprehensive, case-by-case testing is required [5,6]. In the current study we discovered that one of the reason for dissolution profile change is the water content of the powder.

Based on this study, we recommend the measurement of water content and density of mannitol powder before starting further work on it. Also we recommend that mannitol suppliers can add additional test on their quality control steps before releasing the batch for shipment. Also, investigation of probable polymorphism is another challenge for solid dosage forms manufacturers and they should have attention to this matter in addition to the factors mentioned above [7]. In brief pharmaceutical ingredients must comply with well-defined specifications in terms of purity, toxicity, morphology, stability, particle size and solubility [8] and pharmaceutical companies should have full attention to these matters by designing adequate tests.

## CONCLUSION

Attention to all characteristics of mannitol API immediately before use in comparison with zero time quality control results, could be very helpful for making decision during mannitol solution production in pharmaceutical industry.

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