Article

Preformulation Comparative Study between Two Samples of Sorbitol used as Excipient in the Direct Compression Process

Renan Marcel Bonilha Dezena*, José dos Santos Malta Junior
EMS Indústria Farmacêutica, Hortolândia, SP, Brazil

The behavior of pharmaceutical formulations is dependent on the production process, interaction between the excipients and the active pharmaceutical ingredient (API). Therefore it is necessary to carry out a preformulation study for a better understanding of the physical and chemical characteristics that directly affect the stability of the finished product. A preformulation study was performed on the sorbitol present in raw materials from two different manufacturers through the determination of particle size distribution (PSD) by laser diffraction, Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD) and differential scanning calorimetry (DSC). Analysis by FTIR, XRD and DSC showed that there were differences in the polymorphic forms of sorbitol present in the raw materials. The results obtained in the polymorphism tests showed that the first sample of sorbitol raw material contained a stable polymorphic form (gamma) while in the second sample there was a mixture of polymorphic forms (a stable polymorphic form called gamma and a metastable polymorphic form, epsilon). This suggested the need for quality control regarding the type of polymorph to be used in the production of sorbitol formulations to ensure greater therapeutic efficacy.

Keywords — Preformulation, polymorphism, excipients, X-ray diffraction, differential scanning calorimetry.

INTRODUCTION

A complete understanding of the physicochemical properties of a drug substance is the first step in the pharmaceutical study defined as preformulation. Chemical and physical properties are intrinsic to each drug; therefore, solid state characterization will be helpful as an initial analysis. A range of properties can be characterized: organoleptic properties, bulk characteristics (particle size distribution and shape), powder flow properties (such as angle of repose), density, compressibility, crystallinity, polymorphism, hygroscopicity, solubility, ionization constant, partition coefficient, dissolution, drug-excipient compatibility studies and stability [1,2].

Preformulation is useful for a better selection of the drug candidate, formulation components, active pharmaceutical ingredient (API), drug product manufacturing processes, the most appropriate container closure system, development of analytical methods, the synthetic route to the API, the rational development of dosage forms and toxicological strategy. Preformulation studies are important in scientific research because they support the control of the supply of raw materials and preserve resources in drug research and development, thus improving product quality and providing strategies for the formulation process [3-7]. In addition, advances in techniques for characterization of solid dosage forms leads to prediction of physical and chemical stability as a function of preparation and processing.

Polymorphism and pseudo polymorphism are solid state properties that can affect solubility, intrinsic dissolution rates, bioavailability and formulation stability, which are important to the successful development of pharmaceutical products [8]. Fundamental questions include the investigation of polymorphism – the ability of a compound to exist in more than one crystalline form – and careful evaluation of the solid form for development [9].

The difference in entropy associated with physical forms (amorphous, different polymorphs or solvates) leads to measurable differences in physical properties [9]. Two polymorphic forms of sorbitol are known and defined as the (stable) gamma form and the (metastable) epsilon form [10-11].

*renan_marcel@hotmail.com

Sorbitol ($C_6H_{14}O_6$), also referred to as D-glucitol, is widely marketed and disseminated worldwide and has different applications in the food, confectionery and pharmaceutical industries. It is used as an agent in the production of vitamin C and other pharmaceutical products. When exposed to the milling/micronization process many solids undergo direct transformations from a crystalline to a glassy amorphous state, while other crystals convert into a less stable polymorphic form. The structural changes upon milling/micronization increase the number of crystal defects and shear deformations, induced by the mechanical stress. Studies have found that amorphizations are generally observed when milling/micronization is performed below the glass transition temperature of the compound, while polymorphic transformations mainly occur during milling/micronization above the glass transition temperature. This indicates that the thermodynamic principles involved in the amorphic/polymorphic transformation are according to the physics of non-equilibrium phenomena [12-13].

Besides the conversion of polymorphic forms that may occur during the drug manufacturing process, a better evaluation of the raw materials is necessary, since the same molecular compound may already be present initially as a mixture of polymorphic forms, depending on the synthetic route used by the manufacturer. Therefore, prior to the manipulation of the raw material in formulations in the pharmaceutical industry it is essential to characterize its polymorphic form and to enable a better understanding of the predominant factors that have a direct impact on product quality [14].

The study of polymorphism has now become relevant not only in relation to the active pharmaceutical ingredients, but also in relation to the excipients present in the formulation, because they are usually the principal fraction of a pharmaceutical formulation. It is well known that the behavior of the pharmaceutical form is dependent on the production process, the interaction between the excipients, and the impact of the same on the active ingredient and the pharmaceutical form. Excipients previously regarded as simple administration and stabilizing substances of the preparation are now considered to be essential constituents that ensure the performance and safety of the medicinal product and the attainment of the therapeutic effect, and should therefore be the subject of important considerations during the preformulation phase [15-16].

It was possible to perform the physical chemical characterization of sorbitol samples through the determination of particle size distribution (PSD) by laser diffraction, Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD) and differential scanning calorimetry (DSC) [17].

In this work a comparative preformulation study of two samples of sorbitol raw materials from different manufacturers and their possible impact on the direct compression process was carried out, because sorbitol exhibits a polymorphic transformation.

MATERIAL AND METHODS

Samples

The two samples of sorbitol raw material for the direct compression process were obtained from different manufacturers.

Particle size analyses were conducted under the conditions below:

- Analysis module: Dry Powder System (DPS)
- Obscuration: 4%
- Target vacuum: 19 inH_2O
- Sample weight: 3.0 g

Analyses in the infrared region were obtained under the conditions below:

- Germanium crystal with ATR accessory
- Background: 32 scan
- Spectrum obtained: 128 scan
- Resolution: 4 cm^{-1}

Thermal analyses were conducted under the conditions below:

- Initial temperature: 25 ºC

- Heating rate: 10 °C min^{-1}
- Final temperature: 350 ºC
- Nitrogen flow: 80 mL min^{-1}
- Analysis container: 40 µl aluminum (Al)

X-ray diffraction analyses were conducted under the conditions below:

- 2θ: 2 to 40º
- φ: 223.2º
- Variable rotatic [1/min]: 15.0
- Voltage: 30 kV
- Current: 10 mA
- Tube: Cu tube with 1.54184 Å
- Detector: Lynxeye

RESULTS AND DISCUSSION

Determining which critical attributes interfere directly with the quality of pharmaceutical products is crucial in ensuring efficacy and safety, particularly by establishing appropriate limits, range and distribution. Among these critical attributes we can specifically highlight a very important property of the solid dosage forms: particle size distribution [18]. Most of the methods used in the manufacture of API particles involve crystallization processes that generally lead to formation of heterogeneous particle growth, resulting in a variability of particle size [19].

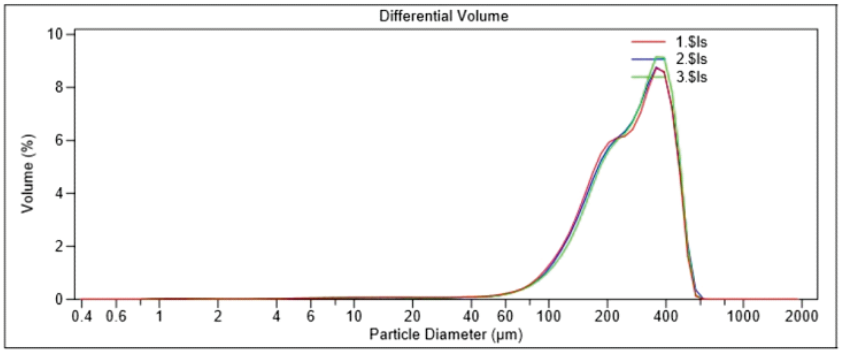
The process known as direct compression represents an interesting option because it allows a reduction in the number of steps and in production time. This process requires high powder flowability and compactability of the active pharmaceutical ingredient and excipients to ensure the consistency of each tablet, so it is necessary to analyze and control the particle size distribution of the formulation components since it directly affects the compaction performance [20].

The samples showed practically the same results of particle size distribution when evaluating the parameters d10, d50 e d90 according to Figures 1 and 2.

It can be verified that the samples presented a coefficient of variation within the specification according to the USP pharmacopoeia (d10 ≤ 15.0%, d50 ≤ 10.0% e d90 ≤ 15.0%) [21].

The particle size distribution was not responsible for the difference between the two sorbitol raw material samples analyzed.

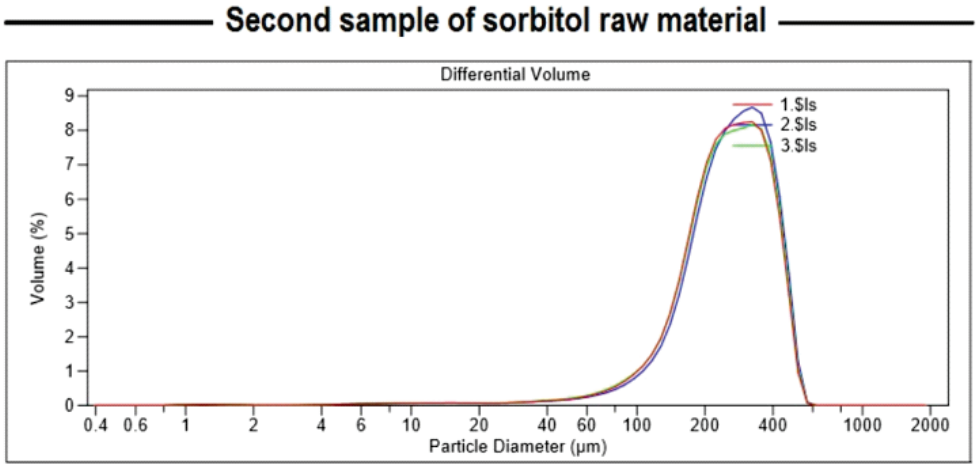
First sample of sorbitol raw material



Volume Statistics (Arithmetic)
Calculations from 0.375 µm to 2000 µm

	Amount %	Mean µm	Median µm	S.D. µm	C.V.	d10 µm	d50 µm	d90 µm
1.$ls	100	271	267	116	42.9%	125	267	430
2.$ls	100	276	273	117	42.2%	129	273	435
3.$ls	100	280	279	116	41.5%	132	279	437
(Average)	100	276	273	116	42.2%	129	273	434
(C.V.)	0.0%	1.6%	2.3%	0.2%	1.7%	2.6%	2.3%	0.8%
(Maximum)	100	280	279	117	42.9%	132	279	437
(Minimum)	100	271	267	116	41.5%	125	267	430

Figure 1. Particle size distribution of first sample of sorbitol raw material.



Volume Statistics (Arithmetic)
Calculations from 0.375 µm to 2000 µm

	Amount %	Mean µm	Median µm	S.D. µm	C.V.	d10 µm	d50 µm	d90 µm
1.$Is	100	262	256	107	40.7%	131	256	408
2.$Is	100	271	266	108	40.0%	137	266	418
3.$Is	100	264	257	109	41.2%	129	257	412
(Average)	100	266	259	108	40.7%	132	259	413
(C.V.)	0.0%	1.7%	2.2%	0.9%	1.5%	3.0%	2.2%	1.2%
(Maximum)	100	271	266	109	41.2%	137	266	418
(Minimum)	100	262	256	107	40.0%	129	256	408

Figure 2. Particle size distribution of second sample of sorbitol raw material.

The technique generally used for raw material identification in the pharmaceutical industry is Fourier transform infrared spectroscopy (FTIR) with attenuated total reflectance (ATR) crystals, which is a simple method of API characterization and identification of solid state properties such as polymorphism [22].

It was possible to observe through the technique of vibrational spectroscopy that the first sample of the sorbitol raw material showed a similarity of 88.03% with the standard while the second sample showed a similarity of 65.79% with the standard (Figures 3 and 4). This difference between the spectra obtained from the two sorbitol raw material samples suggests the existence of a polymorphic transition.

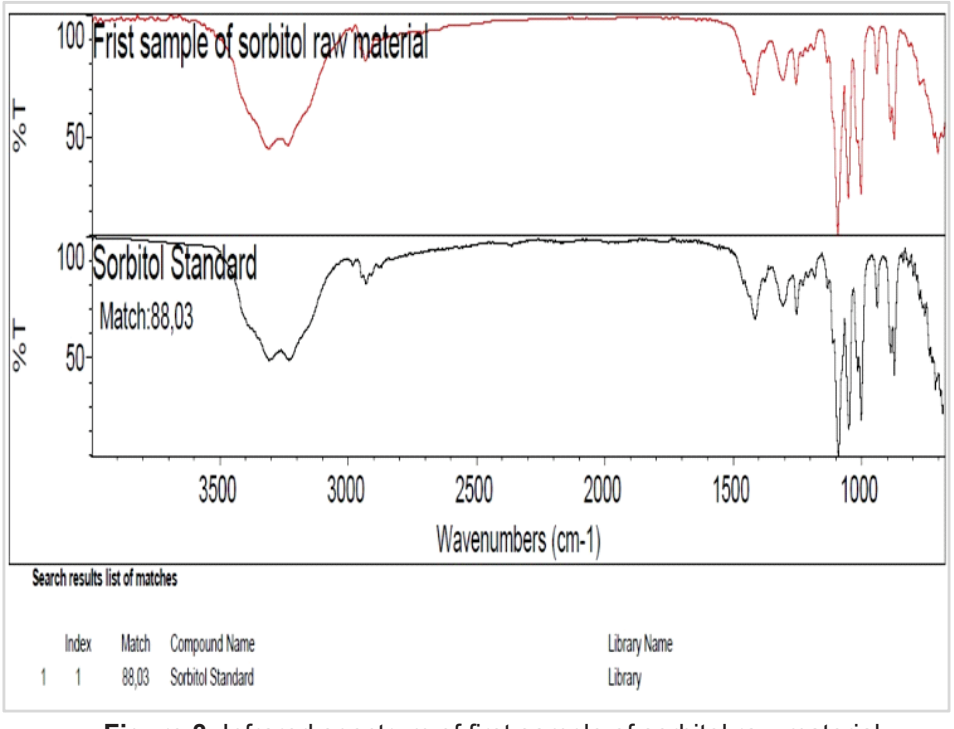


Figure 3. Infrared spectrum of first sample of sorbitol raw material.

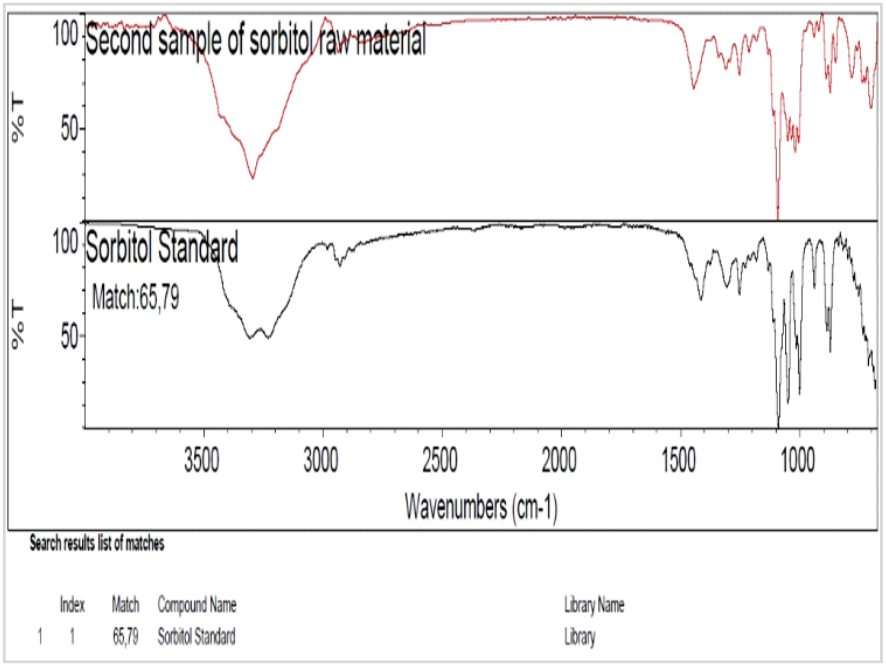


Figure 4. Infrared spectrum of second sample of sorbitol raw material.

When evaluating the diffractograms of the two samples of sorbitol raw material it was found that they showed differences, and that the first sample of sorbitol raw material presented the stable gamma polymorphic form, while the second sample presented a mixture of the gamma form and the metastable epsilon form (Figures 5 and 6). The crystal structures of the pure gamma form pattern and the pure epsilon form pattern were obtained from crystallography open database elucidated by references 10 and 11 using the mercury 3.9 software.

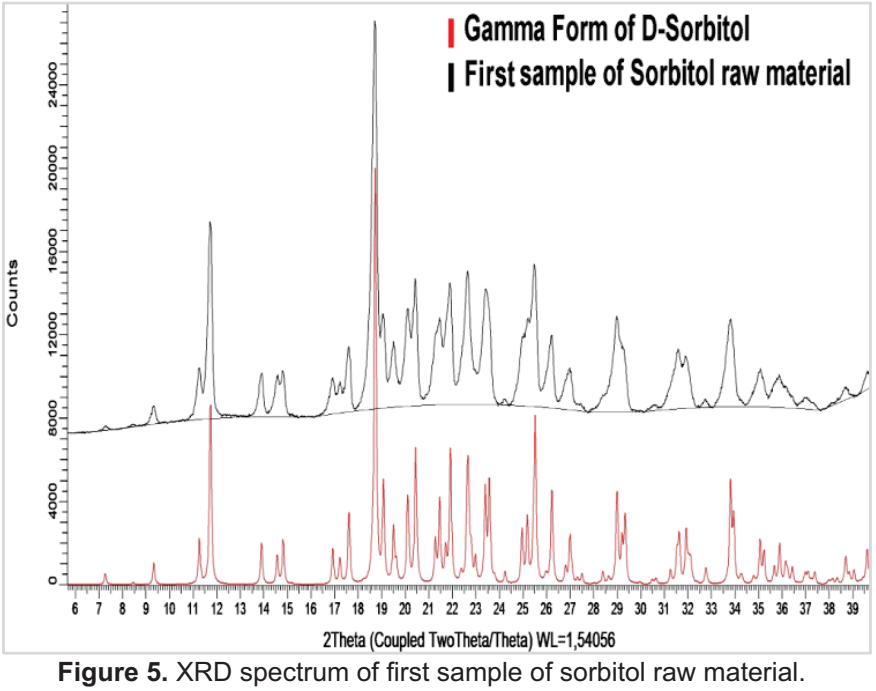


Figure 5. XRD spectrum of first sample of sorbitol raw material.

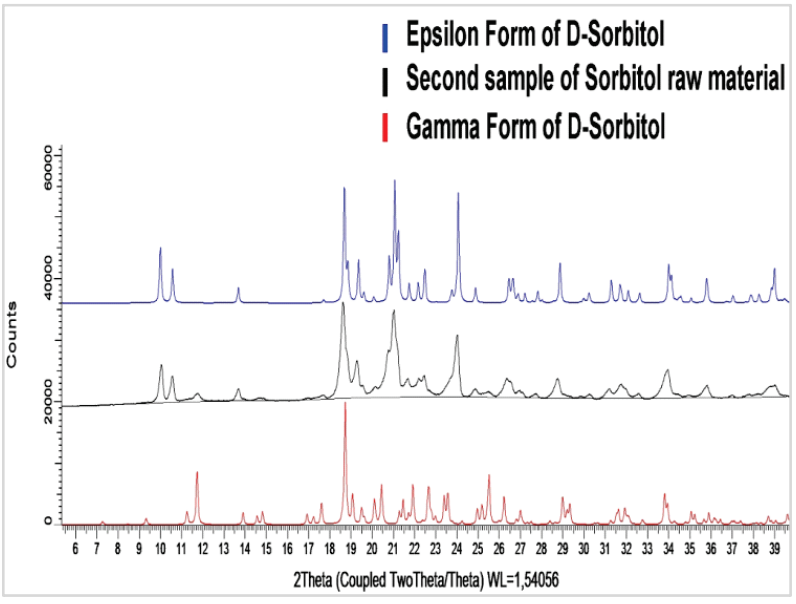


Figure 6. XRD spectrum of second sample of sorbitol raw material.

By analyzing the sorbitol DSC curves (Figures 7 and 8) it was found that the first sample had a well-defined melting point of 99.78 °C because it presented as the stable gamma form, while the second sample had two well-defined melting points at 84.53 ºC and 94.47 ºC, indicating the presence of two polymorphic forms: the stable gamma form and the metastable epsilon form.

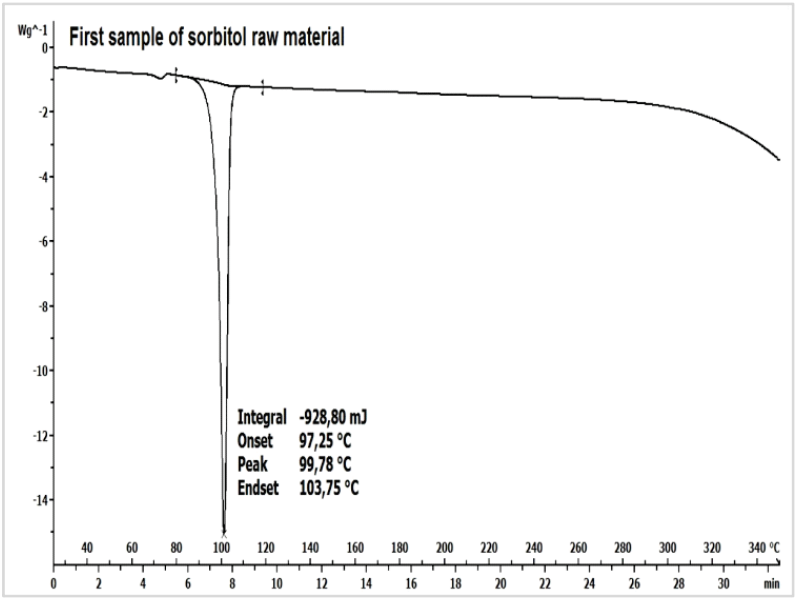


Figure 7. DSC curve of first sample of sorbitol raw material.

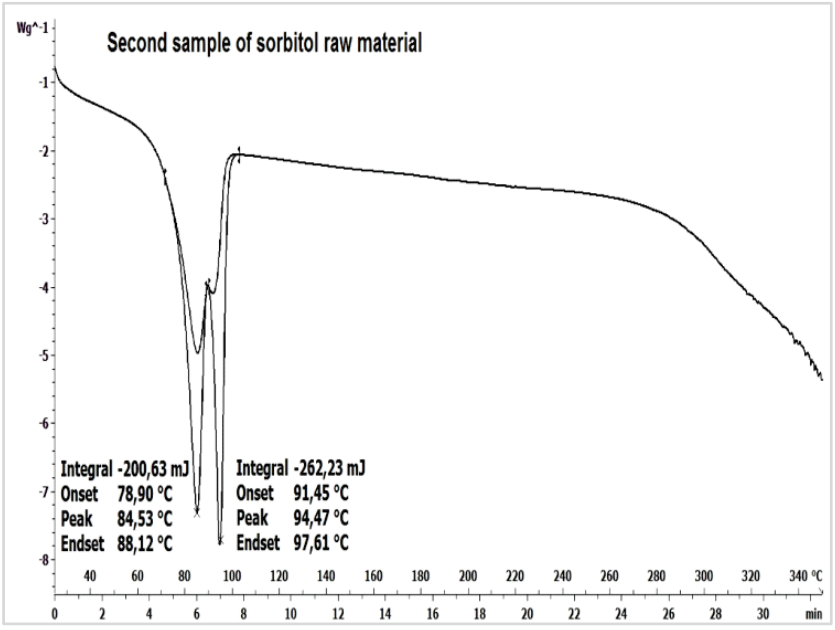


Figure 8. DSC curve of second sample of sorbitol raw material.

The fact that sorbitol presents polymorphism makes this compound susceptible to polymorphic transformations when submitted to mechanical shocks, compression forces and micronization. The glass transition is the transition from the amorphous or semi-crystalline state to the rubber state by increasing temperature and always takes place at a lower temperature than the melting point [23]. Thus a metastable polymorphic form having a lower melting point than a stable polymorphic form will also have a lower glass transition temperature than that same more stable polymorphic form [24-28].

Direct compression is a process causing an increase in temperature due to friction, so if the sorbitol raw material with the metastable polymorphic form (lower glass transition temperature) is used, there will be more adhesion in the punch of the compression machine than when a sorbitol raw material with a stable polymorphic form is used [24-28].

CONCLUSIONS

There have been few studies about transformations induced by mechanical stresses of pharmaceutical excipients.

Solid-phase changes may impact the physical and chemical stability, dissolution characteristics, in vivo performance (bioavailability, efficacy, and safety), which is why controlling solid forms during processing is necessary.

Manufacturing processes in the pharmaceutical industry can induce phase transformations and may be responsible for many observed drug product performance problems.

Experiments performed using PSD, FTIR, XRD and DSC techniques have been helpful in the preformulation studies of two sorbitol raw material samples from different manufacturers.

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