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The characterization and comparison of spray-dried mannitol samples

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Abstract

Background: Following the production of spray-dried mannitol powders, it is essential that the polymorphic content of each individual product is completely characterized. The implications of the polymorphic behavior of mannitol are immense. The appearance or disappearance of a crystalline form within a dosage form can have costly repercussions and lead to a dosage form being withdrawn. *Method*: In this study, commercially available and laboratory-produced spray-dried mannitol products were characterized to establish the polymorphic content of each. Their polymorphic behavior was also characterized after laboratory scale pharmaceutical processes. Thermal analysis employed differential scanning calorimetry, thermogravimetric analysis, and isothermal microcalorimetry. Structural analysis of the samples was obtained using X-ray powder diffraction and Fourier transform Raman spectroscopy. *Results*: Structural analysis revealed that α- and β- polymorphic forms were present in the commercial samples and some contained a mixture of polymorphs. Reprocessing employing spray drying indicated α- to β- polymorphic transitions occurred within some of the samples. *Conclusion*: It is essential that preformulation studies where spray-dried mannitol products are to be employed must take into account its polymorphic behavior upon supply, processing, and subsequent storage.

Key words: *Polymorph interconversion; polymorphic form; spray-dried mannitol; structural characterization; thermal analysis*

Introduction

Mannitol, a hexahydric alcohol, is used in pharmaceutical products primarily as a diluent (10–90%, w/w) in tablet formulations. It is also used in chewable tablets as its negative heat of solution supplies a cooling sensation to the mouth. It is advantageous as an excipient in tablet formulation as it is nonhygroscopic and has an excellent compatibility and safety with drugs[1].

Mannitol is usually supplied as a commercial product in the crystalline form, and several polymorphic forms have been reported in the literature. The numerous polymorphic forms of mannitol that have been described in the literature present a confusing picture as to the number of polymorphs that actually exist. The different polymorphic forms reported[2–7] were examined by Burger et al. (2000), who concluded that three polymorphs exist. These were named modification 1 (β), modification 2 (α), and modification 3 (δ) in line with Walter-Levy's classification[8]. For the purpose of this work, Walter-Levy's system of nomenclature will be used.

The effect of polymorphic changes induced by processing needs to be thoroughly understood when developing new pharmaceutical products as two different polymorphs may be as dissimilar in physical properties as two completely different compounds[9]. The change of crystal form during late-stage development may prove extremely costly both financially and through time loss; therefore, early characterization of any polymorphic changes is essential when developing a new product.

Mannitol is commercially available in spray-dried form for direct compression products. The use of spray drying allows parameters such as particles size and distribution to be controlled. However, it is possible that during the process of spray drying, different polymorphic

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forms or mixtures of polymorphs as well as amorphous material may be produced.

Metastable forms of mannitol may interconvert during processing and storage, resulting in undesirable polymorphic forms being present within the final product. The characterization of these spray-dried products and their polymorphic behavior is therefore essential before they are used in pharmaceutical applications.

The aim of this work was to establish the polymorphic content of several commercial mannitol samples and some of their physical properties upon exposure to different processing conditions and the possibility of their interconversion on storage.

Materials and methods

Materials

- D(−)-mannitol (98–101%)—Merck KGaA, Darmstadt, Germany, Lot No. M205435 206.
- Parteck M 100 (mannitol, 98–101%)—Merck KGaA, Lot No. M287294 349.
- Parteck M 200 (mannitol, 98–101%)—Merck KGaA, Lot No. FF0 19219 218.
- Pearlitol 100 SD (mannitol, 98–102%)—Roquette UK Ltd. (Corby, Northamptonshire, UK) reference 725791, batch E040P.
- Pearlitol 100 SD (mannitol, 98–102%)—Roquette UK Ltd., reference 720151, batch E402M.
- Pearlitol 200 SD (mannitol, 98–102%)—Roquette UK Ltd., reference 727330, batch E014P.

Preparation of spray-dried mannitol

An aqueous (5%, w/v) mannitol solution of each was spray dried using a Buchi 190 mini spray drier. The feed solution was passed through a 0.5-mm diameter atomizing nozzle via a peristaltic feed pump at a flow rate of 13 mL/min. An inlet temperature of 140 ± 2°C resulted in outlet temperatures of 60 ± 3°C. The dried product was collected in a cyclone separator and stored desiccated at room temperature.

Structural analysis

X-ray powder diffraction

X-ray powder patterns were obtained using a Siemens D5000 Difraktometer (Siemens, Erlangen, Germany). The system comprises a scintillation counter detector and a monochromator with a Cu-Kα radiation source ($\lambda = 0.15418$ nm). Samples were placed into a stainless steel sample holder and were subjected to manual compaction to obtain a level surface for analysis. The scanning range used was between 5° and 45° of 2θ with a stepwise scanning mode using a step size of 0.05° of 2θ and a step time of 3 seconds. Sample rotation of 30 rpm was employed during measurements.

Fourier transform Raman spectroscopy

Raman analysis was carried out using an FRA 106 Raman module with a Bruker IFS 66 optics system. The Nd : Yag laser operated at 1.064 μm, and the scattered radiation was detected by a liquid-nitrogen-cooled germanium detector that gave a spectral range of 50–3500 cm^{-1}. Samples were manually compacted into an aluminium sample holder for analysis. A laser power of 900 mW with 500 scans and a resolution of 4 cm^{-1} was used.

Thermal analysis

Differential scanning calorimetry

Differential scanning calorimetry (DSC) measurements were carried out in triplicate using a Perkin Elmer Series 7 DSC thermal analysis system (Perkin Elmer Ltd., Beaconsfield, UK). Samples between 2 and 10 mg were crimped and sealed in aluminium DSC pans with vented lids that were placed in sample cells under nitrogen. Samples were scanned from 25°C to 200°C at 10°C/min.

Thermogravimetric analysis

Thermogravimetric analysis (TGA) was employed to measure mass changes induced by thermal variation to determine the water content of the spray-dried samples. Measurements were carried out in triplicate using a Perkin Elmer TGA Series 7 (Perkin Elmer Ltd.). Solid samples between 2 and 10 mg were loaded onto an open platinum sample pan suspended from a microbalance and heated from 25°C to 275°C at 10°C/min.

Isothermal microcalorimetry

Isothermal microcalorimetry was used to determine the vapor sorption behavior of the samples. Measurements were carried out using a 2277 Thermal Activity Monitor (TAM) operating through 2277-31 Digitam software (Thermometric, Northwich, Sweden). Samples were placed into glass vials with a small glass tube containing water to give a relative humidity of 100%. The vial was crimp sealed with a rubber stopper comprising an aluminium over-seal. The samples were maintained in the measuring position at 25°C for 24 hours.

Scanning electron microscopy

Scanning electron microscopy (SEM) was used to visualize particle surface characteristics and obtain particle size comparisons. Samples were photographed using Hitachi S520 SEM (Hitachi, Tokyo, Japan). Samples were mounted onto a graphite layer on an aluminium stub and gold coated under vacuum using a Polaron SEM cool sputter coater (Polaron, Hailsham, UK).

Processing

Re-spray drying

Spray drying was used to determine the polymorphic behavior of the samples after reprocessing. Spray drying of the samples was carried out as stated in 'Materials and Methods.'

Wet granulation

Wet granulation of the samples was carried out using 10 g of each sample. Water (20%, w/w) was added in three separate portions. After each portion was added, the sample was mixed thoroughly to attain uniform mixing. After all water was added, the samples were allowed to dry for 24 hours at room temperature. Samples were then gently ground in a pestle and mortar to remove large aggregates. The resultant granular mixture was then passed through a size 12 mesh sieve to give uniform particle size prior to X-ray powder diffraction (XRPD) analysis.

Accelerated state stability study

A 2-g portion of each sample was placed in a sample jar in a sealed desiccator containing sodium chloride to give a relative humidity of 75%. The desiccator was then placed into an oven at 40°C. XRPD patterns of the samples were obtained after 1, 2, and 4 weeks of exposure to elevated temperature and relative humidity.

Results and discussion

Structural analysis

X-ray powder diffraction

XRPD is the fastest and most straightforward method of determining the basic information about the structure of a crystalline material[10]. Accordingly, this method was employed to evaluate the polymorphic content of each sample. A reference XRPD pattern of each of the polymorphs is shown in Figure 1, and XRPD patterns of the samples are shown in Figure 2.

The XRPD reference patterns reveal that all three polymorphs have significantly different powder patterns that are listed in Table 1. The powder patterns obtained are in good correlation with those reported in the literature[3,6,11,12]. From the XRPD patterns of the commercial samples shown in Figure 2, it can be clearly seen that there are structural variations between some of the samples indicating that the crystalline structure of the samples is not the same.

From the literature reviewed[6,11–14], it can be concluded that the samples contain two different polymorphic forms. Table 2 summarizes the polymorphic form(s) of each sample.

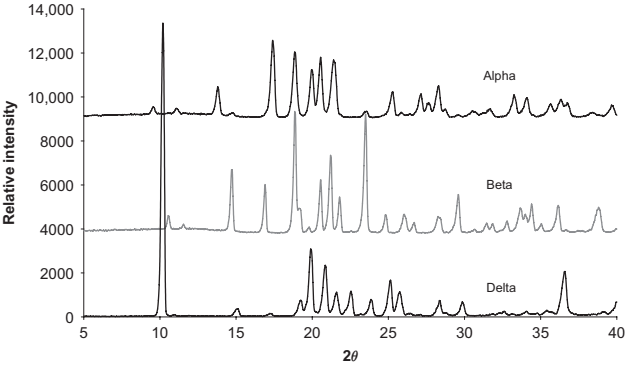

Figure 1. XRPD reference patterns of the three polymorphic forms of mannitol.

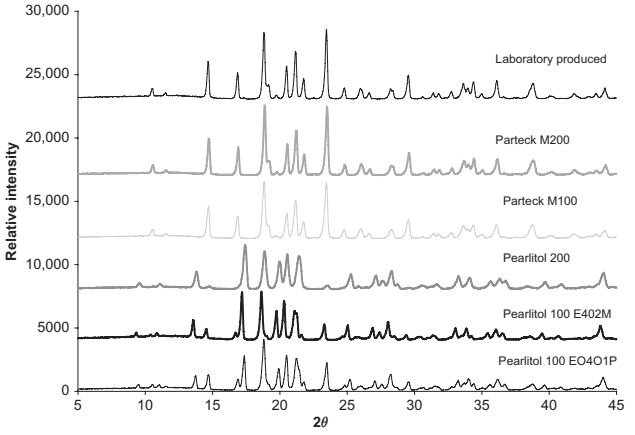

Figure 2. XRPD patterns of commercially available and laboratory-produced spray-dried mannitol.

Table 1. Unique polymorphic peaks in XRPD patterns for mannitol polymorphs.

Polymorph	Position of peak (2θ value)
Alpha	9.57 and 13.79
Beta	10.56, relatively intense peak at 14.71 (this peak is present in alpha and delta polymorph but very weak)
Delta	Extremely intense peak at 9.74 then no peaks until 14.66

Table 2. Polymorphic forms present in commercial and laboratory-produced spray-dried mannitol.

Sample	Polymorph(s) present
Pearlitol 100 (E402M)	α and β
Pearlitol 100 (E0401P)	α and β
Pearlitol 200	α
Parteck M100	β
Parteck M200	β
Laboratory produced	β

Fourier transform Raman spectroscopy

Infrared (IR) and Raman spectroscopies are complimentary techniques that provide structural information on a molecular level. The spectra are based on unique molecular vibrations that occur within a compound; hence the different fundamental molecular vibrations of differing polymorphic forms will give each its own unique fingerprint spectrum from which it may be identified. Raman spectroscopy has the advantage of being able to operate in the 40–400 cm^{-1} region of the spectrum. This region of the spectrum provides information on the crystal lattice vibrations of a sample and is not available on typical IR spectrometers. Consequently, Raman spectroscopy was the chosen method of analysis.

The Fourier transform Raman spectra obtained for the samples are shown in Figure 3. The Fourier transform Raman spectra of the samples confirm the polymorphic assignments from the XRPD patterns. The spectra of the Parteck M100 sample shows a significant intensity increase compared to the other samples. Evaluation of the SEM photographs of the samples showed that Parteck M100 had a much smaller particle size than other samples. Particle size has been shown to affect the Raman signal intensity[15,16]. This reduction in particle size is a possible explanation for the signal intensity increase of the sample.

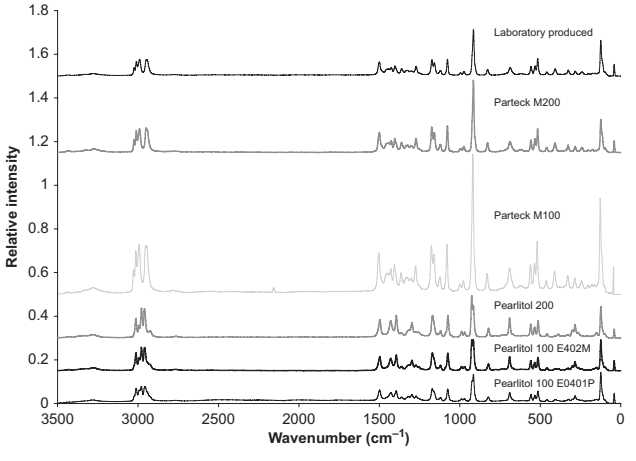

Figure 3. Fourier transform Raman spectra of commercially available and laboratory-produced spray-dried mannitol.

Thermal analysis

Differential scanning calorimetry

A representative DSC thermal profile of a sample of spray-dried mannitol is shown in Figure 4 as all the polymorphs show indistinguishable melting profiles. The thermal profiles of all samples show a single, sharp endothermic peak at approximately 169–171°C

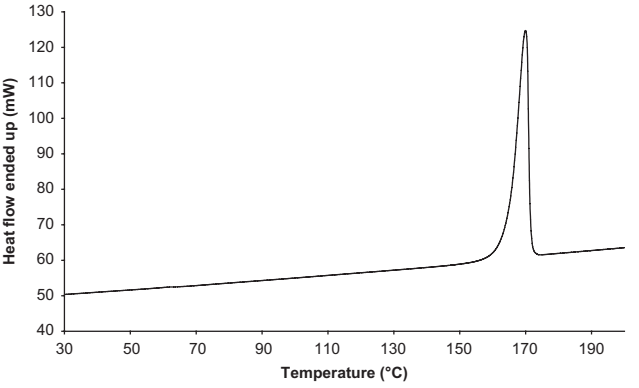

Figure 4. Typical DSC thermal profile obtained for spray-dried β-mannitol.

corresponding to the melting point of mannitol. The average melting point and melting enthalpy for each sample are shown in Table 3. The results indicate that there were no notable differences between the melting points and the melting enthalpies of the samples. This is consistent with the reviewed literature[13].

Thermogravimetric analysis

Decomposition, vaporization, and desorption events are accompanied by mass changes within a sample[17]. TGA analysis was therefore used to determine the decomposition behavior of the samples. A typical TGA thermal degradation profile is shown in Figure 5. The thermal profiles of all the samples are very similar in appearance. The profiles show a minimal weight loss prior to melting and finally decomposition at approximately 190°C.

Isothermal microcalorimetry

Processing conditions and crystallization procedures may induce degrees of amorphous material within a system[18]. Isothermal microcalorimetry was chosen as the method of detection of amorphous material within the samples as the change in heat output upon recrystallization within a sample is directly proportional to the amorphous content of the sample. The lower detection limit of

Table 3. DSC thermal analysis results for spray-dried mannitol samples (n = 3).

Sample	Melting point (°C)	SD	Melting enthalpy (J/g)	SD
Pearlitol 100 (E402M)	171.555	±1.10	268.143	±3.617
Pearlitol 100 (E0401P)	169.722	±1.262	264.255	±3.270
Pearlitol 200	169.889	±1.134	263.222	±2.904
Parteck M100	169.000	±1.093	266.177	±4.311
Parteck M200	169.944	±0.419	276.437	±4.132
Laboratory produced	170.000	±0.601	269.311	±5.219

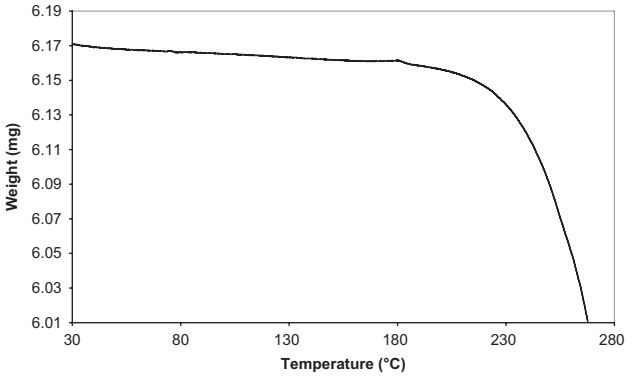

Figure 5. Typical TGA thermal degradation profile of spray-dried mannitol.

amorphous content using isothermal microcalorimetry may be as low as ±0.5%[19]. A typical TAM profile is shown in Figure 6.

The TAM plots of all the samples do not differ notably. After the initial endotherm/exotherm peaks where the sample is lowered into the calorimeter, the baseline remains relatively constant. If any amorphous material was present in the sample, further peaks would be present that indicated thermal events had occurred within the sample.

The plots therefore indicate that there is no amorphous material within the samples; this was expected as pure mannitol does not normally exist in the amorphous state after spray or freeze drying[11,20]. The lack of any thermal events also indicates that α-mannitol does not undergo a transition to β-mannitol. This is consistent with the literature[13]. XRPD confirmed that no polymorphic transitions had occurred within the retrieved samples.

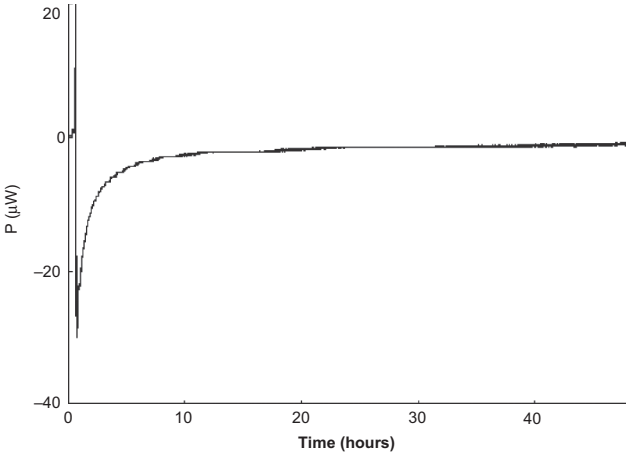

Figure 6. Typical TAM plot of spray-dried mannitol (100% RH and 25°C).

Processing of raw material

Spray drying

Spray drying of the samples was a method of identifying the stability of the polymorphic forms during a commonly employed pharmaceutical process.

The results indicated that after spray drying, all of samples were of the β-polymorphic form only. This demonstrated that the samples that contained the α-polymorph would undergo a polymorphic transition into the β-polymorph under these processing conditions and were therefore unstable for this purpose.

Wet granulation

Wet granulation was employed as a method of identifying the stability of the polymorphic forms under different conditions of spray drying. Figure 7 shows the XRPD of the samples after wet granulation. Figure 7 indicates that all the samples show a notable reduction in peak intensities compared to those of the starting material. It is also significant that the two Pearlitol 100 batches that were initially structurally similar now differ slightly in appearance. The E0401P batch has a more intense pattern with an independent increase in the intensity of the

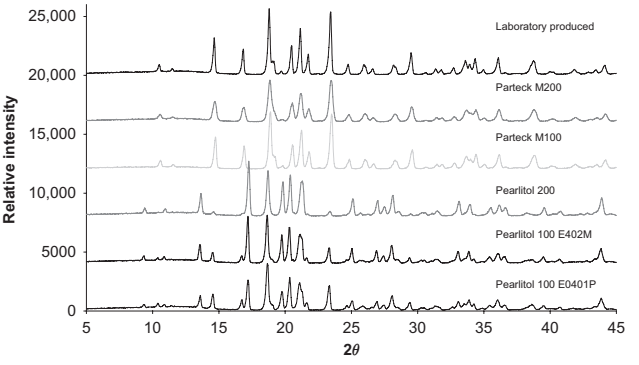

Figure 7. XRPD patterns of spray-dried mannitol samples after wet granulation.

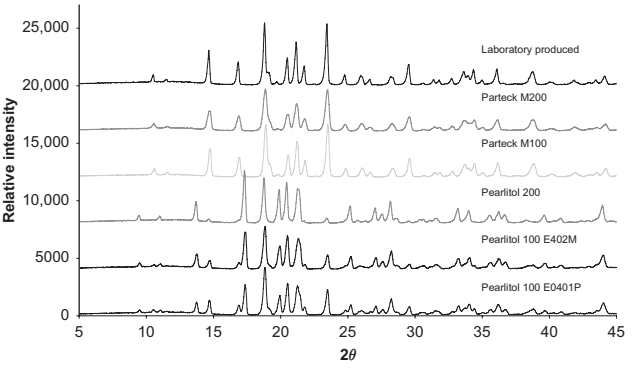

Figure 8. XRPD patterns of spray-dried mannitol samples after 1 week of exposure to elevated temperature and RH.

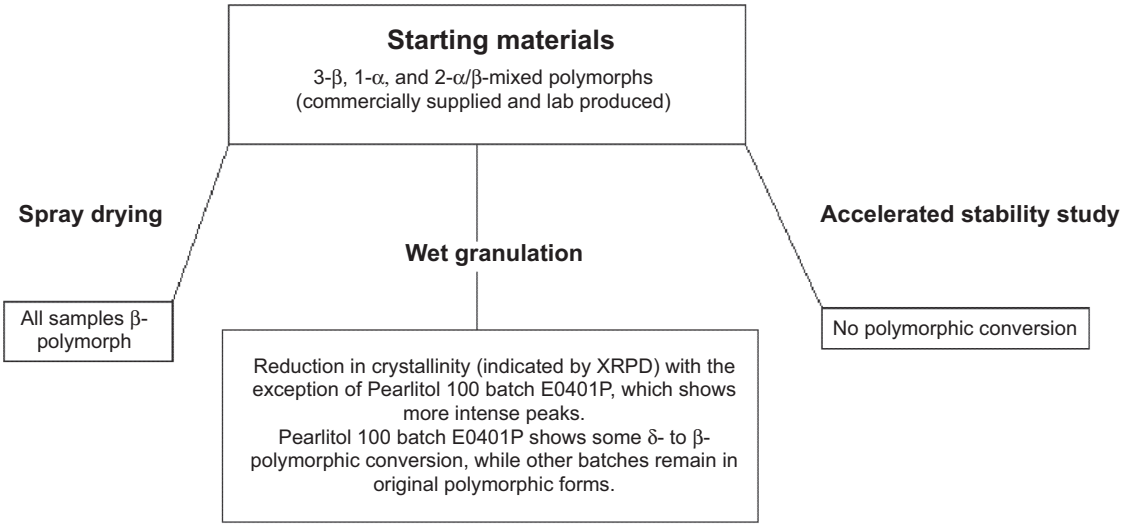

Figure 9. Diagram to summarize reprocessing of samples and effects on polymorphic form.

peaks at approximately 15° and 23° of 2θ and a decrease in the peak at approximately 17.5° of 2θ. This may be due to the presence of two polymorphic forms within the sample in different ratios. The most stable β-form may have a directing effect on the less stable α-polymorph present as the peaks increased in intensity are relatively intense in the XRPD patterns of the β-polymorph and those reduced in intensity are relatively intense in the XRPD patterns of the α-polymorph (Figure 1).

Accelerated state stability study

The use of elevated temperature and humidity was to predict the long-term storage stability of the samples over a short period. Figure 8 shows the XRPD patterns of the samples after 1 week of storage at elevated temperature and RH. From Figure 8, it can be concluded that very similar structural changes have occurred within the samples as those shown in Figure 7. This is also the case after a further week of exposure to elevated temperature and RH.

The XRPD of the samples after 4 weeks of exposure to elevated temperature and RH shows that no structural differences are apparent from the patterns shown in Figure 8. This indicates that at these harsh conditions, the polymorphic content of all of the samples remain relatively stable.

Conclusions

The investigation demonstrated that different commercially available spray-dried mannitol products differ significantly in their polymorphic content. Full structural characterization of each sample is essential as thermal characterization alone did not distinguish the polymorphic differences between the samples. Processing of the samples demonstrated the polymorphic behavior of mannitol with all the samples containing α-mannitol showing some conversion to the β-form, this is summarized in Figure 9.

Declaration of interest: The authors report no conflicts of interest.

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