Drug Development and Industrial Pharmacy, 2011, 37(3): 274–280

ISSN 0363-9045 print/ISSN 1520-5762 online
DOI:10.3109/03639045.2010.509725

informa
healthcare

ORIGINAL ARTICLE

Role of continuous moisture profile monitoring by inline NIR spectroscopy during fluid bed granulation of an Enalapril formulation

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Abstract

Background: Granulation and tableting are closely related process steps in the supply chain of pharmaceutical products. Even today, these steps are still optimized independently by trial and error. On the framework of a process analytical technology approach, these processes were evaluated in an integrated approach. Enalapril maleate is a low-dose drug substance with poor granulating and tableting behavior. In order to verify how granulation influences tableting properties, different granulation experiments were performed. *Methods*: Granulation experiments with fast spraying rate and fast drying as well as fast spraying rate and slow drying, and also combinations of both were run. The obtained granules were then promptly compressed into tablets in a rotary press and subjected to hardness testing. The progress of spraying and drying was controlled by a continuous near-infrared spectroscopic measuring setup. This study confirms that the tablet characteristics. *Result/Conclusion*: after compression of the granules in comparison to placebo granules are dependent not only on the residual moisture content of the granules but also on the moisture profiles during the entire fluid bed granulation process.

Key words: Enalapril maleate formulation, fluid bed granulation, moisture profile, process analytical technology, quality by design, tablet compression

Introduction

In the production of solid dosage forms such as tablets, granulation is a process step of size enlargement of fine particles into larger particles for improving flowability and compressibility. Granulation can be performed by fluid bed processing. Many parameters may affect the granule properties and consequently the resulting quality of the tablets—therefore this is a complex process[1].

Knowing the effects of these parameters including their interactions and also understanding the granulation process are essential conditions for controlling it and hence the resulting outcome[2]. The near–infrared (NIR) reflectance method is an analytical investigational tool for increasing insight into the granulation process. Monitoring the moisture content online during granulation may be important because the water content does not only have a direct impact on the granule properties but also an indirect effect on subsequent process steps.

It is known that the residual moisture of granules influences tablet properties such as breaking strength (hardness), friability, and disintegration time[3]. The purpose of this study was to investigate the role of the moisture trend during the entire granulation process as an additional parameter for the characteristics of Enalapril maleate tablets.

Enalapril maleate is an angiotensin-converting enzyme inhibitor used in the treatment of hypertension. It is effective in lowering blood pressure and has cardioprotective potential[4]. The properties of the chemical and physical stability of Enalapril maleate tablets have been described previously[5].

There are many studies dealing with the influence of process parameters in fluidized bed granulation on granule properties[6–11] to determine optimum process

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(Received 10 Feb 2010; accepted 15 Jul 2010)

conditions for a high-quality product. Up to now, there have been no studies on Enalapril maleate, a very difficult active pharmaceutical ingredient (API) in terms of processing for solid oral dosage forms, which results in high batch-to-batch variability of physical tablet stability and tableting behavior when compressed from its granules. In fact, the Enalapril formulation showed the mentioned effects against placebo control formulations even though only 2% of API were present in the formulation.

Several of these studies are in line with the concept of the Food and Drug Administration's Process Analytical Technology (PAT) initiative[12]. PAT is a risk-based approach; it is strongly linked to the ICH Q8(R2), Note for Guidance on Pharmaceutical Development[13] approach. The general idea of this approach is the improvement of production quality at lower costs, also enabling the change of manufacturing variables during the lifecycle of a product[13]. Therefore, the rapid introduction of new technologies, for example, NIR spectroscopy is encouraged to understand the process as well as the inline control to reduce the requirement for end-product release testing. The major aspect to follow this learning curve is to identify the critical process parameters (CPPs), first. Therewith, it is essential to appraise the influence of the CPPs on critical quality attributes on each single process step[14]. Critical quality attributes are product characteristics that should be within an intended specification range to maintain the overall product quality. Typical attributes of solid dosage forms are, for example, moisture content and particle distribution of granules or tablet hardness, which are picked out as central themes in this study. In the example given here inline process control is used to better follow the granulation process using state-of-the-art analytical technologies. This improved knowledge can lead to lower manufacturing costs caused by a predictable product quality.

The present granulation experiments have been performed to discriminate the total exposure of the granules to humidity during the entire process as given by the moisture profile and maximum moisture value during processing from the usually employed residual moisture content of the final granulation product. The particle size distribution was maintained virtually constant in this study.

Materials and methods

Instrumentation

The fluid bed granulation trials were performed in a Hüttlin Unilab® (Hüttlin GmbH, Schopfheim, Germany). A NIR spectrometer model X-One® (NIR Online GmbH, Walldorf, Germany) was used for continuously monitoring the inline moisture content during the granulation process. The special design of the Unilab®, which implements the efficient air distribution plate, DiskJet® allows the installation of the NIR device directly on the product container without the risk of blocking the window with product dust. The granules are fluidized in a uniform and harmonized way so that the product cleans the NIR window itself continuously during the process.

The Manesty laboratory R&D rotary tablet press XS-Press® (Knowsley, Great Britain) equipped with round concave punches and dies with a 6-mm diameter was used for compression of tablets from the granules obtained. The compression force was adjusted to 15 kN, and the average weight of the compressed tablets was 118 mg. For the determination of the tablet hardness (breaking strength) an Erweka TBH 210 TD (Erweka, Heusenstamm, Germany) was used.

A volumetric DL38 Titrator (Mettler Toledo, Gießen, Germany) as well as the reagents Hydranal® composite 5, Hydranal® Methanol rapid, and Hydranal® water standard 10 were used for Karl Fischer titration.

Particle size measurements were performed using an inline particle size measuring system (Parsum GmbH, Chemnitz, Germany). The measuring principle is an extended spatial filter method based on evaluation of the shadows of a laser beam that are created by particle movement. No calibration is needed, because the Parsum probe is based on a direct measurement.

Materials

Enalapril maleate (USP grade) was obtained from ANDENEX-CHEMIE (Braunschweig, Germany). Lactose monohydrate was purchased as Granulac® 200 from Meggle (Wasserburg, Germany). The granule formulation consists of 2% API, 84.5% Lactose monohydrate, 11% maize starch, and 1.5% sodium hydrogen carbonate. The granulation liquid consists of API and sodium hydrogen carbonate dissolved in purified water. Magnesium stearate 1% was used as glidant and was added after the granulation step just before tablet compression.

Karl Fischer titration

The moisture content of the granule samples for calibrating the NIR was measured using a Mettler Toledo DL38 Titrator with dry heat oven Stromboli®. The samples were weighted in a glass and sealed with an aluminum cap. The moisture in the samples was expelled by heating to 140°C for 900 seconds and transferred by a nitrogen flow into the titrating cell of the DL38 in which the water determination was performed. By heating the samples to 140°C, the crystal water from lactose monohydrate is not extracted[15].

The Karl Fischer test is designed to determine water content in samples utilizing the quantitative reaction of water molecules with iodine and sulfur dioxide in the presence of methanol and pyridine organic base. The amount of iodine consumption as a result of reaction with water in a sample is measured.

The samples for Karl Fischer analysis were withdrawn throughout the granulation processes which were performed before running the experimental granulation batches. The samples were taken directly out of the fluid

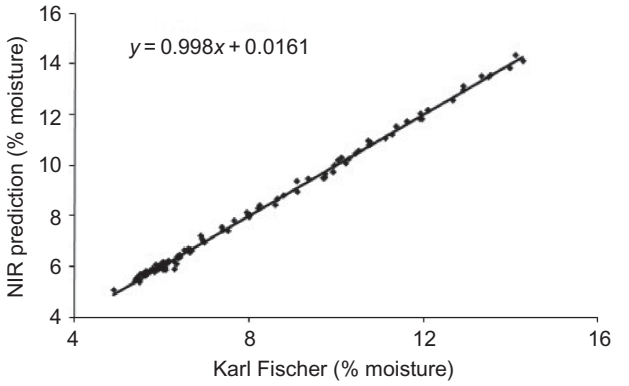

Figure 1. Relationship between water content determined by NIR and Karl Fischer titration for Enalapril maleate formulation using 100 reference samples.

bed granulator's container in the same height as the NIR device is placed. Hundred samples were measured with Karl Fischer and the calibration curve (Figure 1) was generated. A correlation coefficient of 0.10% and a standard error for the calibration of 0.13% were achieved.

Two additional batches were run to validate the model. Twenty-seven samples were taken from the process and analyzed by Karl Fischer titration. The obtained standard error of prediction for validation was 0.12%.

The standard error for calibration is calculated using the following equation:

$$s = \left[\frac{1}{(n-1)} \times \sum (x_i - x)^2 \right]^{1/2}$$

The term $(x_i - x)$ symbolizes the residuals between the NIR value and the value from Karl Fischer analysis, whereas n symbolizes the total number of measured samples, namely 100 for the calibration set and 27 for the validation set. This standard error can also be used to estimate the standard error of prediction.

An accuracy test as presented in Figure 2 was obtained from the data of the two validation batches

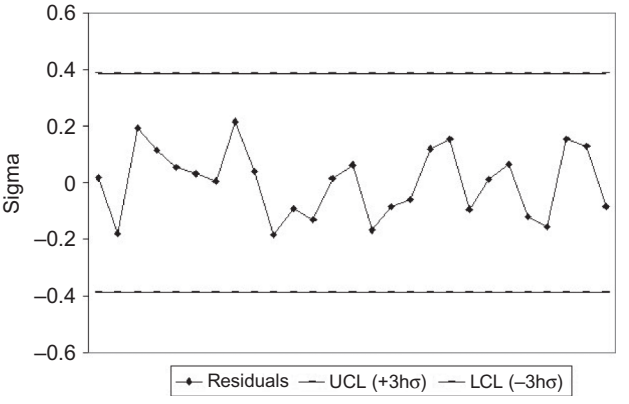

Figure 2. Accuracy test for the calibration of the Enalapril maleate formulation obtained from 27 validation samples.

where the residuals, that is, the differences between the Karl Fischer reference value and the predicted NIR value are plotted. It is obvious that the NIR calibration obtained is very robust as no outlier was detected and all residuals (difference between Karl Fischer and NIR value) are located within the 3σ region (99.7% confidence interval based on the standard error of prediction).

The 3σ region is defined by the value of the standard error of calibration multiplied by a factor of 3. This means that 99.7% of the predicted NIR values from the calibration set has a maximum deviation of 3σ from the average value and therefore are following the 3σ rule.

Granulation procedure

The starting solid materials were suck into the fluid bed after the product container was preheated. Mixing took place until the desired product temperature of 28°C was reached. This took about 10 minutes after which the spraying of granulation liquid commenced. The inlet air volume was set to 200 m^3/h and was not changed during the process. For obtaining a low-moisture profile, the spray rate was adjusted to 80 g/min and the inlet air temperature to 65°C, respectively. For obtaining a high-moisture profile, a spray rate of 80 g/min at the beginning of spraying process, which was decreased to 30 g/min at the end of the spraying period, and an inlet air temperature of 30°C were adapted. All other process parameters, for example, inlet air humidity and atomizing pressure, remained constant in all batches. The granules were dried within the instrument for variable periods of time which was controlled by use of inline NIR measurements. The granulation end point was reached at defined residual moisture contents of 6% and 8%.

Results and discussion

Insufficiency of granule residual moisture content as predictor for tablet hardness

To investigate whether the moisture content and manufacturing process of granules are the parameters with major influence on physical tablet quality, four different granule batches were produced: two of them with a residual moisture content of approximately 6% and two with 8%. The maximum moisture content during granulation was similar in all four batches. The major difference in processing of the four granule batches was the duration of exposure of the granules to a defined moisturous environment during granulation. By variation of two process parameters of fluid bed granulation, different moisture profiles can be obtained.

One granulation batch with 6% residual moisture content and one granulation batch with 8% residual moisture content was exposed to a low-moisture profile, whereas the other two batches were exposed to a high-moisture profile. Low-moisture profiles were obtained with fast spraying rate and fast drying at high inlet air temperatures of 65°C, whereas high-moisture profiles

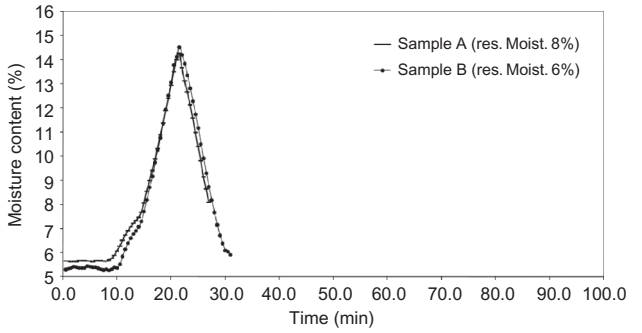

Figure 3. Moisture content versus time curves for the two granule batch profiles with a low-moisture profile. Sample A: granule sample with a residual moisture content of approximately 8%; Sample B: granule sample with a residual moisture content of approximately 6%.

were obtained with fast spraying at the beginning of the spraying step that was decreased to slow spraying rate at the end of the spraying step combined with slow drying at low inlet air temperatures of 30°C.

Figure 3 shows the time versus moisture content curves for the two granule samples with low-moisture profiles but different residual moisture contents.

Both granule batches were compressed into tablets. The two tablet samples were then subjected to hardness testing immediately after compression. The sample exposed to a low-moisture profile with a high-residual moisture content (Figure 3; Sample A: fast spraying) broke into small pieces directly after ejection from the die of the tablet press. This sample failed the hardness test, but the tablets obtained with the same process but lower residual moisture content (Figure 3; Sample B: fast spraying) passed the test with a breaking strength of about 80 N.

The formation of granules in a fluid bed system starts with spraying an aqueous solution onto the product bed. Initially water is adsorbed onto the surface of the granules followed by its partial evaporation. The granule growth mechanism is controlled by the equilibrium between wetting and evaporation of the powder bed[16]. The formation of the typical bramble structure of a granule and of agglomerates is determined by the building of liquid bridges, when two or more solid particles coincide with a liquid droplet. As the liquid evaporates during drying of the granules, the liquid bridges are transformed into solid bridges[17] under simultaneous reorganization of the agglomerates. Whereas spraying and adsorption develop in gas phases with high diffusion coefficients, the formation and agglomeration of granules can be assumed to occur on a much longer time scale. The granulation process is considered to be controlled by the slowest step, which means by the formation and merger of single particles into granules.

For samples with low-moisture profiles within a rapid granulation process, the time for diffusion of water into the granular structure and consequently the formation of liquid bridges is short. Considerable amounts of water cannot be integrated into the granules and are rapidly removed by drying. The described water absorption properties of the granules essentially influence the granule growth mechanism[18]. When water cannot penetrate into the granule, then it is expected to be only adsorbed on the surface of the granules, which leads to a granule product showing inferior tableting properties. This hypothesis was tested using Samples A and B.

Sample A with high residual moisture content and a low-moisture profile has more water adsorbed on the granule surface compared with Sample B with low residual moisture content and likewise low-moisture profile. During the compression step, the 'surface water' has no plastic deformation properties and the energy from deformation will be released during ejection from the die of the tablet press. This leads to a breakage of the tablets and therefore a failed hardness test for Sample A.

Influence of granulation total process moisture exposure on tablet hardness

To investigate the effect of total process moisture exposure of the granules, the granule moisture profile was varied whereas the residual moisture content in two batches was adapted to the same value.

Figure 4 shows the two moisture profiles of the granules both containing a residual moisture content of approximately 6%. In Sample B fast spraying was produced straightforward in about 30 minutes whereas in Sample C slow drying was produced with nearly the same maximum in moisture content but with a three times extended granulation time because of slower drying. Samples from B with a low-moisture profile and a low residual moisture content have little water adsorbed on the surface of the granules, as described before, whereas for the samples from C with a high-moisture profile and likewise low residual moisture content the water had time enough to partially diffuse into the structure of the solid granule particles and to form liquid bridges. Granules with a higher diffused water content in their structure are thus leading to semihard tablets because the embedded water can expand during compression

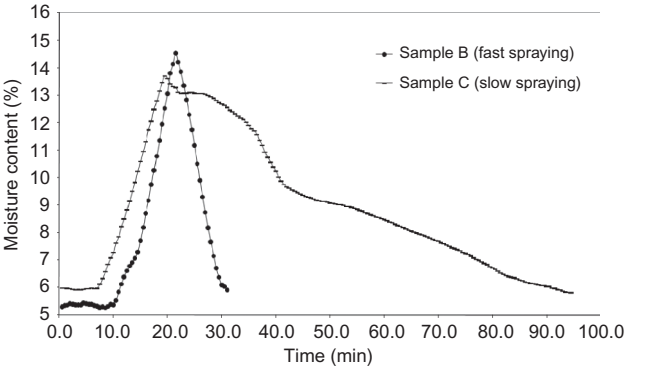

Figure 4. Moisture content versus time curves for the two granule batch profiles with a residual moisture content of about 6%. Sample B: granule sample with a low-moisture profile; Sample C: granule sample with a high moisture profile.

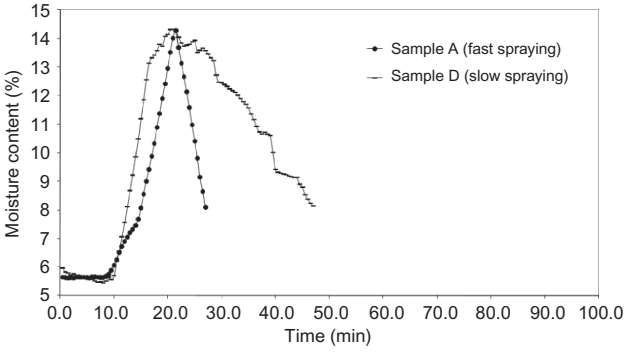

Figure 5. Moisture content versus time curves for the two granule batch profiles with a residual moisture content of about 8%. Sample A: granule sample with a low-moisture profile; Sample D: granule sample with a high moisture profile.

and has no opportunity to diffuse, whereas water that is only on the surface of the granules may still diffuse into the tablet during compression. This confirms the model of slower integration of water into the granules structure compared with the gas-phase diffusion-controlled fast adsorption process.

For validating this hypothesis, the same procedure was also followed for the granules showing a higher residual moisture content of approximately 8%. In Figure 5, the two moisture profiles of these granule samples with different moisture profiles are shown. Again, the maximum moisture content during granulation was maintained and the granulation time was increased by nearly a factor of two (Sample D: slow drying) as expressed by the corresponding increase in moisture profile.

In Sample D slow drying with a high-moisture profile and a residual moisture content of approximately 8% achieved a breaking strength (hardness) of about 40 N, whereas in Sample A fast spraying with a low AUC and likewise a high residual moisture content of 8% failed the hardness test, as described before. These results again indicate that the granulation process of the Enalapril maleate formulation is kinetically controlled in terms of exposure to moisture, and the residual moisture content of the product is only relevant when the time for granule formation, that is the duration of exposure of the granules to a defined moisturous environment during the fluidized bed process, is too short for obtaining high-quality granules and accordingly high-quality tablets. A prolonged exposure of the granule samples to certain moisture content (high-moisture profiles) with defined maximum moisture exposure value was found to exert a strong influence on the resulting quality of the tablets.

Granulation is a process step to increase particle sizes for improving flowability that is important for subsequent process steps. Therefore, also the particle size distribution of the granule samples has been analyzed. Particle sizes and particle size distributions were maintained as similar as possible for all batches.

Selected characteristics of the obtained granules and tablets, average particle sizes (D50), moisture profiles, maximum moisture contents during granulation, residual moisture contents of the granules, and breaking strengths (hardnesses) of the obtained tablets are as summarized in Table 1.

The moisture profile can be declared as a relevant critical process control parameter for the granulation of Enalapril maleate formulation. Maximum moisture content during granulation and a certain range of residual moisture content are additional factors for tablet hardness that need to be specified within a given range. Using this information, a design space can be set up as given by ICH Q8(R2)[13]. At this point, it seems to be realistic that even with very difficult formulations the granulation and tableting process can be understood and standardized by a quality by design (QbD) approach.

Additional granulations were performed with different moisture profiles and variations of the maximum moisture content during the granulation process as well as different residual moisture contents. In Figure 6, the moisture versus time profiles during granulation for these experiments are shown.

As the maximum moisture content during the process exceeds 16% and a residual moisture of about 8% is present, as in Sample E (Figure 6) the tablets were found to break into pieces directly after ejection from the die of the tablet press. Samples from Sample F with almost the same moisture profile as Sample E and likewise a residual moisture content of approximately 8% resulted in a breaking strength of 20 N, which is too low for practical purposes but not as inferior as Sample E. This again confirms the above-mentioned hypothesis and indicates that the whole granulation process and thereby a process control using a PAT regime is advantageous.

Conclusions

Granulation and tableting are closely related process steps in the supply chain of pharmaceutical products.

Table 1. Overview of the different granule sample characteristics and properties.

Sample/Properties	D50 (μm)	Moisture profile	Maximum moisture content (%)	Residual moisture content (%)	Tablet hardness (N)
Sample A	98	Low	14.26	8.08	n.a.
Sample B	107	Low	14.52	5.90	80
Sample C	117	High	13.68	5.81	40
Sample D	103	High	14.31	8.13	40
Sample E	108	High	16.94	8.00	n.a.
Sample F	106	High	15.13	8.42	20

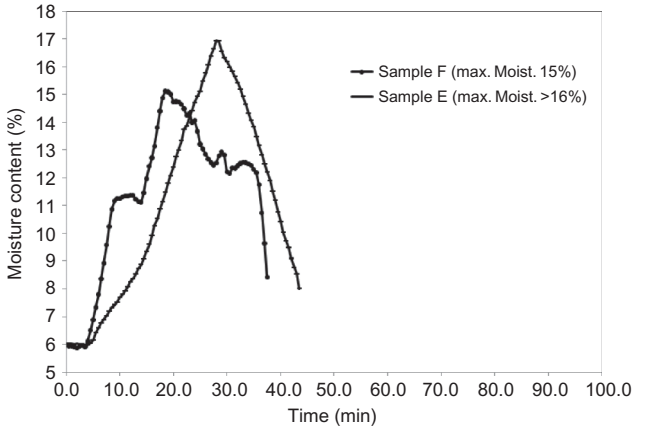

Figure 6. Moisture content versus time curves for two granulation batches with different moisture profiles and a residual moisture content of about 8%.

Even today, these process steps are still optimized by trial and error.

On the framework of a PAT approach, these two steps were evaluated together with respect to the effect of the moisture influence on granulation and tableting. NIR has been shown to be a powerful PAT tool. A systematic scientific approach for the evaluation of the two process steps using this PAT tool has been demonstrated as an opportunity to gain process knowledge, which can be used to control and predict the quality of the product. The found control has the potential to monitor critical as well as limiting parameters influential to the combined granulation and tableting process as a QbD approach. This applies for the Enalapril maleate formulation only, but the general principles can well be expected to become relevant also for other granulation processes, because the CPPs are identified, the variability can be controlled by the PAT regime, and the product quality can be predicted. For new products, this general approach also might be used to create a design space of materials and process parameters, which will lead to a more robust and flexible regulatory submission.

The moisture profile for the Enalapril maleate formulation seems to be only important when the residual moisture content exceeds 6%, because in this case the time for diffusion of the water into the granule structure becomes important. A low-moisture profile—meaning a short time for diffusion—leads to a higher water deposition on the surface of the granules. A high-moisture profile—meaning a longer time for diffusion—leads to higher water content within the structure of the granules.

A value of the maximum moisture content >16% during granulation is found to be absolutely critical to the process as well as limiting the maximum moisture content to a value below 16%. Besides that as process control tool in the sense of PAT, the profile of the moisture has also been identified as important. A successful strategy for real-time process control of granulations of the Enalapril maleate formulation therefore should include an inline moisture measurement setup with boundary values for maximum moisture, residual moisture content, and a moisture profile control even with a moisture profile optimization.

Thus, it is necessary to mention that not only residual moisture in granules may have an impact on subsequent process steps such as tableting and the resulting physical characteristics such as breaking strength (hardness), friability, and disintegration time, but also the trend of the moisture profile during the entire granulation process. It should be considered that the moisture is of indispensable importance throughout the entire wet granulation process in the fluidized bed.

It was demonstrated that the whole loop of QbD using systematic optimization can lead to process understanding, a clear design space, where the intended product quality can be achieved and the setup of a PAT tool can be closed. Although this is only a first example, it shows that process understanding in pharmaceutical manufacturing is possible and will lead to more robust processes that allow higher quality products at lower overall costs.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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