

X-Ray Net Weight Control of Pharmaceutical Products

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Abstract

Pharmaceutical manufactures have to ensure that their medication contains precisely the stated quantity of material and active product ingredient (API), so the industry's quality control standards are very high. The initiative "Process Analytical Technologies" (PAT), driven by the American food and drug administration (FDA), addresses this task and the improvement of inline inspection systems. To achieve this, a new method has been developed at Bosch Corporate Research for the inline net weight control of pharmaceutical capsules in packaging machines, which shows potential for high accuracy. The method measures the intensity of an x-ray beam that is passed through a capsule. From the attenuation of the beam the exact mass in the sample can be calculated, which makes it an alternative to the conventional process of weighing the sample using a load cell. The x-ray procedure has been automated and is very precise. The thickness variation in the bottom of the capsule is nearly negligible, so the system can be described as a net-weight control system. Reference measurements are taken to compensate for any drift in the method's sensitivity. As pharmaceutical companies produce large quantities of such capsules, the process has been created with up to 18 parallel x-ray sensors to operate simultaneously to assure short cycle-times. The system is housed in a shielded enclosure, so radiation cannot penetrate to the outside and the x-ray intensity is so low, that it has no effect on the medication, as confirmed by inspections conducted in-house and by independent external specialists. Patients can be confident: All capsules are tested 100% to ensure they hold the correct mass.

Keywords: x-ray, weight, mass detection, pharmaceutical products, inline process control

1. Introduction: Why does the Industry need PAT ?

Manufacturing technology in the pharmaceutical industry is not yet operating at the level the FDA would like to see, where development is mostly driven by the start of production (SOP) and the necessity to get a product to the market fast, to benefit from it before generic products appear. As described by Afnan, A.^[1], after the regulatory approval is given, the industry is often satisfied with a 2 sigma process as opposed to the 6 sigma process attempted elsewhere. Whilst the approval and documentation is carried out thoroughly, it would be important actually to push manufacturing innovations and ensure a better process understanding to ensure high quality products for the customer. This is why the initiative PAT was started and its primary focus is to achieve a better process understanding. The actual FDA definition is ^[2]

- PAT is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

According to the FDA the term *analytical* in PAT is to be viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner.

The European medicine agency (EMA) is supporting this initiative as well and the pharmaceutical industry is picking up the methodology, not all of which's techniques are new, but often the 100% in-line inspection or timely sample measurements which ensure short quality control cycles, can still be optimised in production.

2. Overview on Process Analytical Technologies (PAT)

The definition, as given by the FDA^[2], is rather broad and includes:

- Multivariate data acquisition and analysis tools
- Modern process analysers or process analytical chemistry tools
- Process and endpoint monitoring and control tools
- Continuous improvement and knowledge management tools

From these PAT tools, as the Robert Bosch GmbH is a producer of packaging machinery, the main focus amongst the critical parameters is on the quantity, or product mass, and the content, or active product ingredient (API) of gelatine capsules. The measurement tools to analyse the manufacturing process can be grouped into mechanical (energy, temperature, pressure, flow, mass) and physical/chemical (UV, NIR, MIR, Raman, THz, spectroscopic microscopy, x-ray, optics, acoustics etc.) tools, as described by Reich, G.^[3]. This paper then focuses on the development of an x-ray measurement tool, to be placed among the physical inspection technologies, to measure the mass of pharmaceutical products.

3. Measuring the Weight of Pharmaceutical Products with X-Rays

3.1. Problem Formulation

One of the main PAT tasks is the identification of the correct mass of pharmaceutical products. This paper describes the development of a measurement system using x-rays to measure the precise weight of the content in gelatine capsules. The task in particular requires the in-line measurement of the net weight of the substance that is filled into gelatine capsules, typically powder, pellets or micro tablets, and functions reliable for 100 % inspection in cycle times of less than a second. The x-ray system therefore is an innovative alternative to the existing mechanical weighing process using load cells, which is a separate process step.

3.2. Measurement Principle

The basic measurement principle is quite straight forward as shown in Figure [1]. The packaging machine fills a capsule with a specified substance, then passes it through an x-ray beam for inspection and finally closes the capsule. From the absorption of the x-ray beam that has passed through the capsule, the exact mass can be calculated.

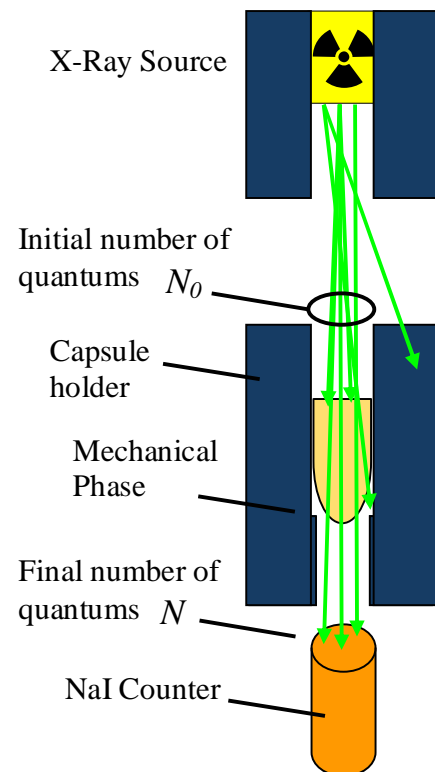


Figure [1]: Measurement Principle

This method is so precise in fact, that due to the negligible thickness variation at the bottom of the capsule, the system is a net-weight measurement system. Any rays which would pass through the side walls of the capsule are shielded by the mechanical phase of about 0.3 mm at the bottom of the capsule holder. Any scattered rays are blocked by the metal capsule holder. The measurement system uses an extremely small x-ray source, about the size of a finger, which is used in the range from 20 to 40 kV. This ensures the necessary but minimal radiation intensity to measure the mass of the substance in the capsule in transmission and yet produces absolutely no significant influence on the capsule substance.

The Sodium Iodine detector produces an electric current, corresponding to the radiation intensity at the bottom of the capsule holder and runs with a sampling rate of 2000/s. The effective measurement time is a quarter of a second, as only the time without movement is considered for measurements and the packing machine can run production with a cycle time of up to 140 tacts/min. Thus, the detector does take 500 measurements in a quarter of a second and calculates the result as the mean value of these measurements.

Each test measurement is followed by a reference measurement for continuous monitoring of the system. The x-ray beam is testing a synthetic material in-between the capsule measurements to compensate for any drift in the methods sensitivity over time. Whilst continuous drift monitoring allows for the compensation of e.g. any flux in the energy supply, initial calibration is still necessary, to set up the measurement system correctly. As the absorbance depends on the product that is being filled into the capsule, the system needs calibration with samples about 10% overweight, samples on target and samples filled 10% below target, to produce the calibration curve. The calibration curve is linearised (or approximated by a first order curve), in the surrounding of 10% of the filled weight. Thus, the system measurements are true within this range, as the machine achieves an accuracy of 2 %, as described later. For values that are more than 10% away though, it is only valid to say that the capsules hold not the correct mass any more, but no absolute values can be given. Calibration is necessary for every change of product, this being one of the requirements of the system.

The absorption of x-rays corresponds directly to the mass of the object it is penetrating, according to the physical law of Lambert-Beer-Bouguer ^[4]. For monoenergetic radiation it is defined

$$\frac{N}{N_0} = e^{-\mu_{[E,Z]} \cdot \rho \cdot d} \quad (1)$$

where, N_0 is the number of individual quanta before the object,
 N is the number of individual quanta after the object,
 ρ is the density,
 d is the length (or thickness) of the object in direction of radiation, and
 $\mu_{[E,Z]}$ is the absorption coefficient (material and energy specific).

Furthermore, the area related mass can be calculated as density times object length, and thus the object mass can be calculated as follows,

$$\text{area related mass } m_A = \rho \cdot d \quad (2)$$

$$\text{mass } m = m_A \cdot A = \rho \cdot d \cdot A \quad (3)$$

and thus, the final equation which gives the correspondence between mass and absorption can be formulated as,

$$m = -\frac{1}{\mu_{[E,Z]}} \cdot \left(\ln \frac{N}{N_0}\right) \cdot A \quad (4)$$

Though the background physics on this topic are quite well known, the main difficulty remains in applying this theory successfully to an in-line machine measurement system, which has a good robustness, and functions reliably under the given boundary conditions of a capsule filling machine. Thus, the specific usage in a packaging machine and certain construction elements are also formulated in a patent application^[5].

4. Application of the X-Ray System to a Packaging Machine

4.1. Measurement System Construction

The initial system is constructed as a single channel prototype with only one x-ray source and one detector to demonstrate the measurement capabilities of the system. An impression of the packaging machine itself is given by Figure [2]. The measurement station is placed after the capsule filling station, and before the closing station, to measure the weight of the powder in the open capsule. The x-ray source and the detector feed their information directly into the machines central software, where the data is processed, so any faulty capsules could be ejected from the machine.



Figure [2]: Capsule Packaging Machine

4.2. Single Channel Measurement System

The single channel system was built up at the corporate research headquarters of the Robert Bosch GmbH, at Gerlingen Schillerhöhe, Germany.

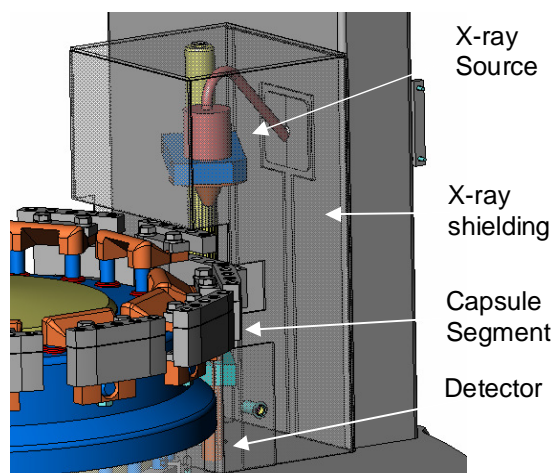


Figure [3]: Single Channel Construction

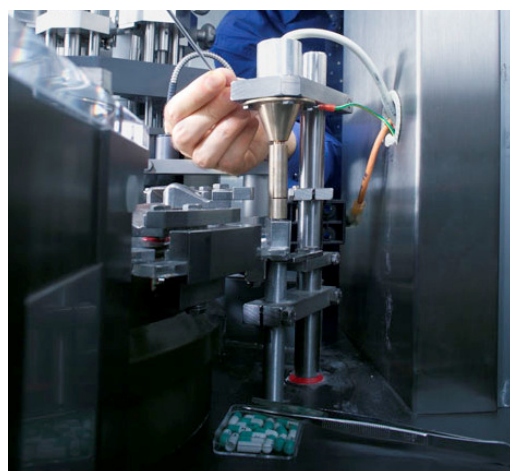
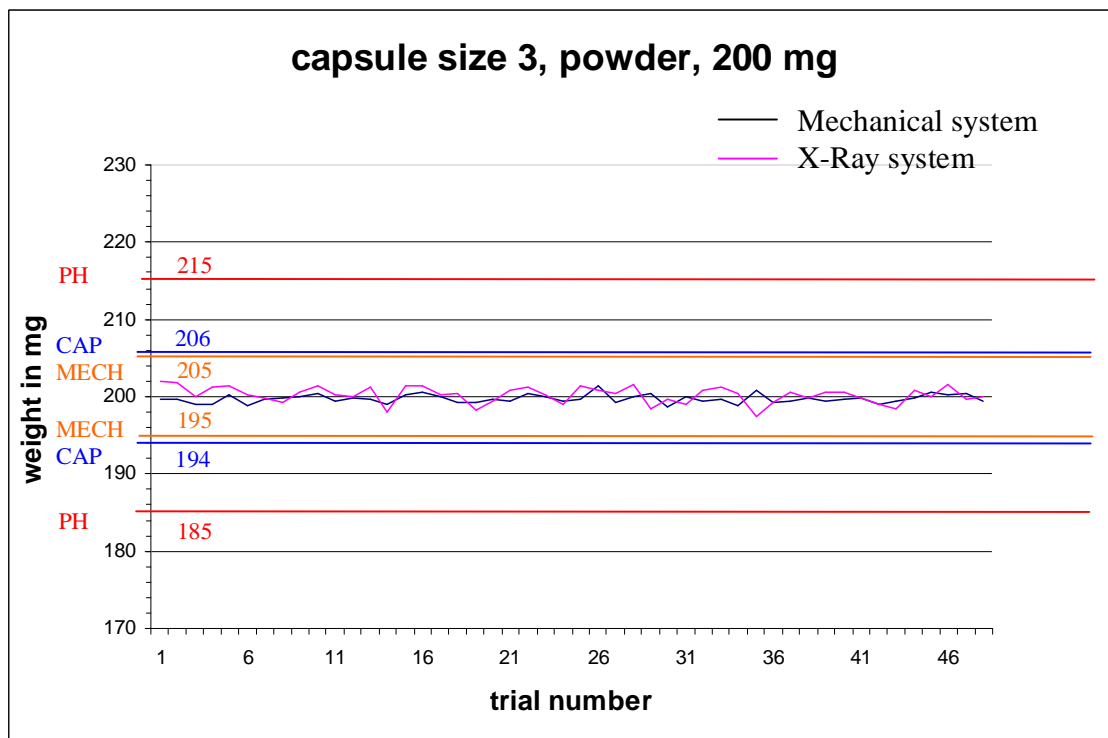


Figure [4]: Single Channel In-line System

For this initial system the measurement results were not yet processed by the central machine software but by a separate measurement PC programmed in Labview. Figure [3] shows the CAD construction and Figure [4] then the actual system in the machine with the shielding removed.

4.3. Accuracy of the Measurement System

The accuracy of the measurement system depends on the weight that is to be detected and has to be calibrated for each product, as the individual substance absorbance depends on the characteristics of the atoms present. We have achieved an accuracy of 2% of the filling weight between 20 mg and 500 mg filling weight, which has been proven by a series of test measurement experiments. Thus, for the example of a filled weight of 200mg, the measurement could vary by +/- 4mg. For very small filling weights, 1 mg to 10 mg, the measurement is more difficult, but the x-ray technology still shows an innovative potential to achieve the accuracy asked for by the pharmaceutical industry. Current research investigates the use of different detectors. Figure [5] shows the measurement results for the example of lactose powder filled in capsules of size 3 with a mass of 200mg



Standard Deviation Mechanical System:	Standard Deviation X-Ray:	Min/Max Deviation X-Ray:
0,535 1sigma	1,076 1sigma	min -3,25 mg
1,606 3sigma	3,227 3sigma	max 2,47 mg

Figure [5]: Accuracy of the X-Ray Measurement system

Capsules come in a size range from zero to five, zero being the largest. The capsule size has no influence on the measurement taken, a mid-range value chosen for this experiment. Each capsule was measured by the x-ray system as well as a mechanical system. The graph shows the result for 48 individual measurements. The results show that the x-ray system stays well within the

given three tolerance bands of: the pharmaceutical industry standard (PH) of 7.5 % deviation, a capacitive measurement system (CAP), and the mechanical system (MECH) that is used so far.

The tolerance band is set at $\pm 5\text{mg}$, because although the load cell has an accuracy of $\pm 2\text{mg}$. This is done, because the mechanical system is not a net-weight measurement as compared to the x-ray measurement system and therefore the tolerance band is adjusted. After the measurement principle with the single system prototype was proven, by various test series each time just changing one parameter of the system, it became clear that a robust measurement solution was found. In the next step, the construction had to be carried out for multi-channel system, to be able to have a 100% in-line inspection system. Depending on the machines production capabilities the system therefore has to be scaled up, and we chose to carry this out for the GKF 2500 machine (Capsule Filler 2500), which requires the system to measure 18 channels in parallel. This system then was built up at the business unit Packing Technology (PA) of the Robert Bosch GmbH, located in Waiblingen, Germany.

4.4. Multi Channel Measurement System

The multi-channel system prototype can be seen in Figure [6]. The multi-channel system has obviously stricter boundary conditions than the single system prototype, starting with the installation space, cycle time, reference measurement setup, the temperature problems when 18 x-ray sources are running in parallel and the signal processing, just to mention a few examples.

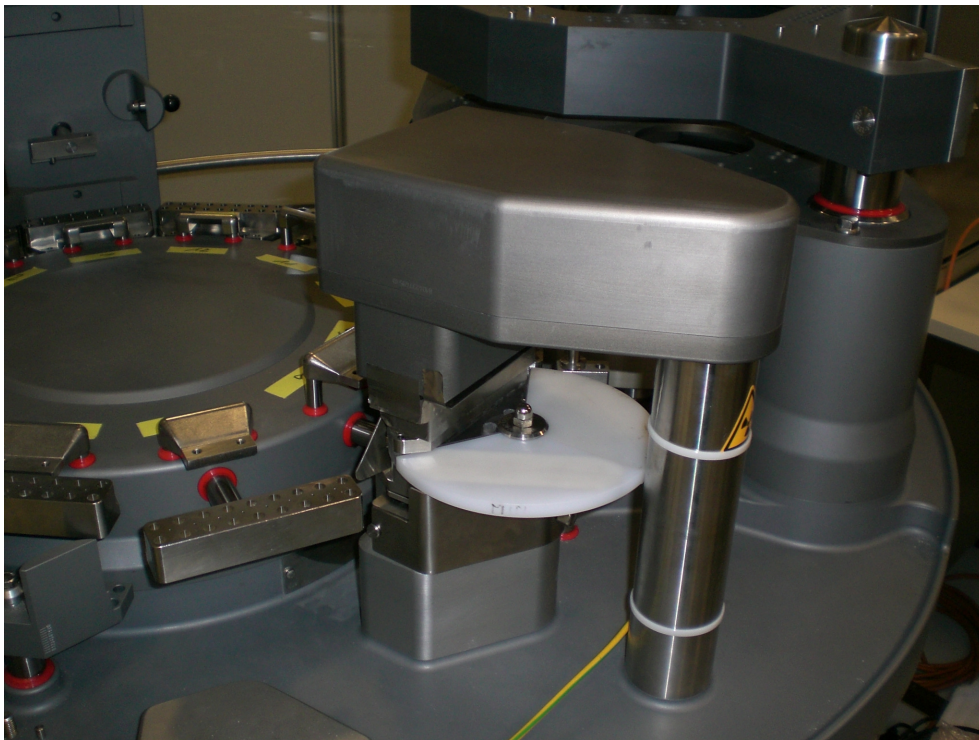


Figure [6]: Multi Channel In-line X-Ray Measurement

Nevertheless, those challenges were overcome and the first system is this year being produced at our business unit, the first system actually being sold to a pharmaceutical customer, see also^[6]. The system is also suitable for the production of toxic medical products, washing-in-place and cleaning-in-place procedures can be installed easily, as the measurement system can be housed-

in completely. Furthermore, as the system is housed in a shielded enclosure, no radiation can penetrate to the outside, which is ensured by two separate switches, which turn off the x-ray source if either the machine door is opened, (not the shielded enclosure which is only removed during maintenance) or the system stands still for more than one second.

4.5. Product Safety

In-house studies as well as externally conducted expertises have concluded that in the worst possible case, a capsule would be exposed to a radiation dose so low, it would pick up the same dose similarly by natural radiation, if stored under normal conditions for several weeks. To be more precise, the number of atoms affected would be 2.5 ppm in the worst case scenario, whereas in a more realistic scenario the number is even less than 0.1 ppb. The calculation for the worst case scenario is as follows: if we consider that each quantum has an energy of 33 eV, and each quantum that is not arriving at the detector would pass its energy to molecules in a harmful way, (the effect of the interaction not necessarily being negative) then only 2.5 ppm of the molecules would be affected. Furthermore, every such molecule would have to be API, where normally the percentage of fillings, such as lactose, is much higher than the actual API. In fact, x-ray treatment of products for sterilisation is carried out as a standard procedure with up to 100.0 mGray, this value being allowed by the regulatory bodies, whereas our system uses only 0.23 mGray for the measurements.

5. Summary, Future Trends and Requirements

In this paper we have described the need for process analytical technologies (PAT) in the pharmaceutical industry, to ensure good quality manufacturing and process understanding. This includes the control of critical parameters with timely measurements, to which the quantity (mass) and the active product ingredient (API) of a product undoubtedly belong.

We have developed a new x-ray net weight control system, which measures the mass of gelatine capsules packed on the machines of the Robert Bosch GmbH. This innovative measurement system is non-destructive, non-evasive and ensures 100% in-line inspection in cycle times of less than a second. It uses less space than the separate step of a mechanical weighing system and has a high accuracy. As the system is housed in a shielded enclosure, no radiation can penetrate to the outside and the x-ray intensity is so low that it has no effect on the medication, as described earlier.

The central question concerning the future of process analytical technologies is really whether the regulatory bodies will move from an encouraging but voluntary industry guidance to a stricter enforcement in the regulatory process of pharmaceutical product approval. To predict any such step would be entirely speculative, although the customers would receive better quality products. But no matter whether voluntarily or enforced, it should be in the pharmaceutical industries own interest to pick up PAT tools for the manufacturing process.

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