

Chemometrics (PCA) in Pharmaceutics: Tablet Development, Manufacturing and Quality Assurance

Ingunn Tho¹ and Annette Bauer-Brandl²

¹*University of Tromsø*

²*University of Southern Denmark*

¹*Norway*

²*Denmark*

1. Introduction

Pharmaceutical tablets are subject to special regulations regarding their quality. Obvious examples are requirements for tablet performance in terms of pharmacological effect, which is closely connected to the uniformity of drug substance content in each tablet, to the disintegration properties of the tablet into smaller particles after intake, and to the rate of dissolution of the drug substance from the tablet or particles (drug release). For each product on the market, a set of quality criteria and their specific limits are defined by the relevant regulatory health authorities, e.g. Food and Drug Administration (FDA) in the USA, or European Medicines Agency (EMA) for Europe.

Following the steps of the development of a new tablet, we distinguish six main phases:

- a. design and synthesis of the new pharmaceutically active drug substance (active pharmaceutical ingredient, API),
- b. characterisation and quality assurance of the bulk raw materials, i.e. the API and additives (excipients),
- c. optimisation of the composition of the formulation with respect to API and excipients,
- d. scale-up to larger throughput (industrial scale),
- e. optimisation and validation of the processing steps for the manufacturing; monitoring processing steps during manufacture,
- f. quality assurance of the finished product, the tablet.

Tablets have been produced for more than 100 years in large quantities, and their quality has always been an issue; therefore the technical factors that influence tablet properties have been studied extensively. It has immediately become obvious that the number of factors is large and that there is a lot of interaction between them. Therefore, pharmaceutical development in general, and tablet manufacture in particular, have been one of the first areas where factor analysis and Design of Experiments (DoE) have been introduced.

The current international regulations for pharmaceutical products, namely the ICH (International Conference of Harmonisation) guidelines (ICH Q8) including Quality by

Design (QbD) approaches together with Process Analytical Technology (PAT) initiated by the FDA in 2004 have drawn even more attention to the use of state-of-the-art science and technology (PAT-Initiative, 2004; Guidance for industry, 2004). Improvement of the manufacturing of drug preparations is thereby initiated with the aim to replace end-product control of random samples by real-time quality control of every single item.

It is nowadays a prerequisite for the registration of a new tablet preparation to show how the use of systematic studies during the development phase has led to a good understanding of the processes, how rational decisions have been made during the development process with regard to an optimum product, how the manufacturing processes can be controlled within set limits, and to estimate the robustness of the processes, i.e. what a certain variability of any ingoing parameters means for the properties of the final product. Therefore, it is very common to integrate factor analysis and multivariate projection methods such as PCA in all stages of pharmaceutical development and manufacture in general. However, tablets are a particularly prominent example thereof, because all stages from the preparation of the bulk powder, granulation, compression and coating widely influence the properties of the final marketed product. Systematic studies within a reasonable design spaces and a good scientific understanding of the processes reduce uncertainty and create the basis of flexible and risk-based regulatory decisions. Therefore, chemometric methods, such as DoE and multivariate analysis (MVA) are – if nothing else of necessity – frequently and extensively used in pharmaceutical product and process development.

This chapter focuses exclusively on fundamental studies for the rational development of tablet formulations of general interest. Therefore, it will restrict to examples of commonly used excipients and to simple manufacturing methods. The interested reader is addressed to specialized textbooks for further reading about production technologies and quality assurance (e.g. Bauer-Brandl & Ritschel, 2012; Gad, 2008).

2. Definitions and background information

2.1 Pharmaceutical tablets

Tablets contain both the active pharmaceutical ingredient, API, for obvious reasons, and different types of excipients to generate both manufacturability and product performance. In a standard procedure, both types of powders (API and excipients) are homogeneously mixed and granulated, the granules finally mixed with more excipients (glidants, lubricants, etc), upon which the final blend is compressed into tablets. The tablets will, in contact with water or fluids of the gastrointestinal tract, disintegrate into the granule/powder again, before the drug substance is released. Figure 1 depicts the basic steps of production of a standard tablet and processes upon contact with water or gastrointestinal fluids.

2.2 Quality of tablets

For pharmaceutical tablets, quality has many aspects: We have to distinguish between the tablets as such, and the drug product, which includes the packaging and the product description. Table 1 lists some of the most important quality criteria for a tablet product. Any of these may be used as a quality attribute for optimisation of a tablet product.

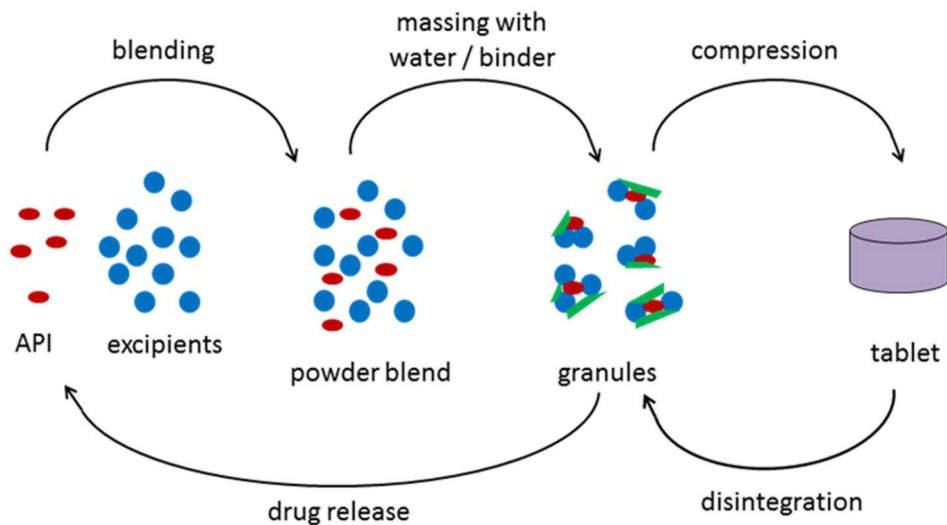


Fig. 1. Schematic drawing of the basic production steps of a tablet (upper arrows), and the disintegration and release of drug from the tablet (lower arrows)

<i>Appearance of the tablets</i>	<i>Composition</i>	<i>Properties of the tablets</i>	<i>Properties of the drug product</i>
Shape	Identity of drug substance(s)	Mechanical strength	Outer package identity
Dimensions: Height, Diameter	Additives (excipients)	Ease to break	Label identity
Engravings (Symbols, numbers, etc)	Quantitative drug content per tablet	Disintegration behaviour in water	Leaflet identity
Colour	Total mass per tablet	Drug release rates in different media	Tamper-proof inner package
Surface appearance (shiny, smooth)	Coating composition	(mouth feeling)	Safe storage conditions
No specks, no spots	Coating thickness	No capping, no layering	No sign of tampering
No cracks, no chipping			No defect

Table 1. Some important quality criteria of tablets as a drug product

For the marketing of a drug product, all the specifications need to be authorized by the respective local health authorities. Thereby, the actual values of quality requirements are defined for each single product individually, depending on the significance of the different criteria for this particular product and on special rules in the respective country.

2.3 Tablet development

The development of a new tablet formulation and production process takes its start in the properties of the active ingredient(s). For formulation (composition) development, it is of importance to choose the most suitable set of excipients to mix with the APIs to obtain a tablet product of certain quality attributes. In process (handling) development, including the choice of the processing method, all the processing parameters (such as temperatures, sequence of addition of excipients, mixing conditions, duration of the processing steps etc.) contribute to rather complex interrelated relationships between critical process parameters and quality criteria. The entire production process is typically divided into several steps, each of which is individually optimised.

Figure 2 shows general principles of how to control step-wise production. Choice of production method, optimisation of production steps, and control schemes have traditionally been handled by practical experience and by empirical development methods.

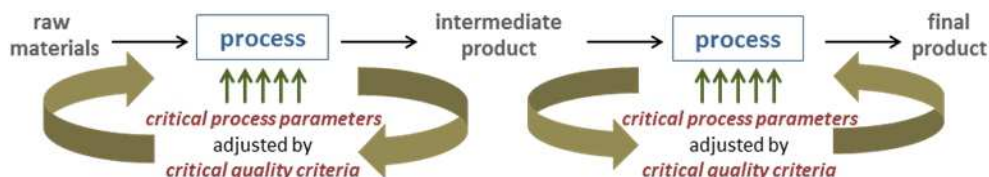


Fig. 2. Schematic drawing of production step control

2.4 A Brief overview of processes and parameters involved

In the following the elaboration will be restricted to basic tablets produced by a standard technique. Table 2 shows the impact of the main production steps on the quality of standard tablets. A schematic depiction of the sequential arrangement of some commonly used processing steps for standard tablets is given in Figure 3 together with a selection of related important processing parameters. Furthermore, monitoring of some machine parameters is also included.

2.5 The combination of DoE and MVA

Statistical experimental design, also called design of experiments (DoE), is a well-established concept for planning and execution of informative experiments. DoE can be used in many applications connected to tablet development and manufacture. One may, for instance, use designs from the *fractional factorial* or *central composite* design families, when addressing problems in which the influence of process parameters (temperature, pressure, time, etc.) on product properties are monitored and optimized. Another main type of DoE application concerns the preparation and modification of mixtures or formulations, where the challenge is that the parameters are not independent but components add up to 100%. This involves the use of *mixture designs* for changing composition and exploring how such changes will affect the properties of the formulation (Eriksson et al., 1998). Also designs in which both process and mixture factors are varied simultaneously are frequently seen. For tablet development and manufacture, one or several of the process parameters and/or critical quality attributes listed above, are likely to be used as optimization goals.

Tablet Property	Raw materials	Granulation	Drying	Final blending	Compression
Dimensions	++	+	+	+	++
Appearance	+	+	++	+	++
Total mass per tablet	+	+	++	++	-
Drug content (assay)	+	+	+	++	-
Mechanical strength	++	++	++	++	++
Disintegration	++	++	+	++	++
Drug release rate	++	++	+	++	++
Stability; degradation	+	-	++	-	-
Microbiological quality	++	-	++	-	-

+: important; ++: very important; -: important in special cases only

Table 2. Impact of Processing Steps on Tablet Quality

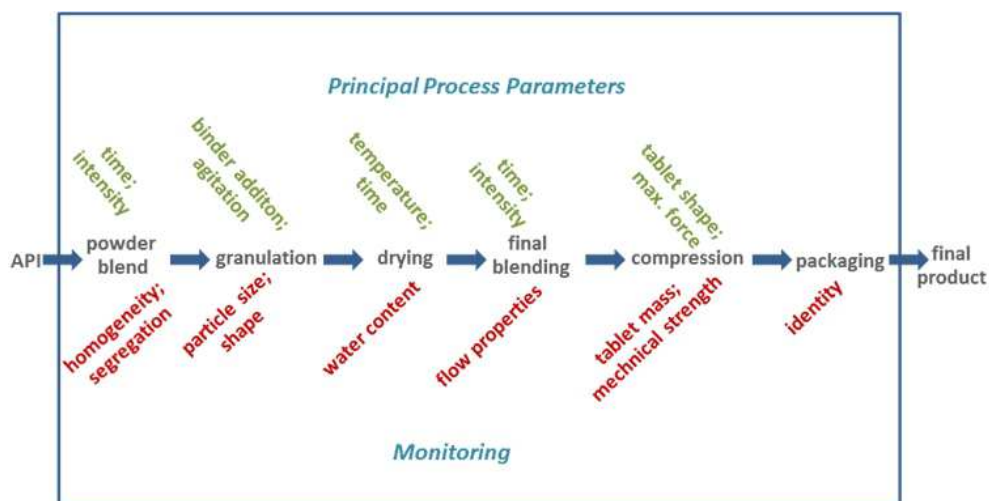


Fig. 3. A schematic view of the course of main processing steps, processing parameters and monitoring features of tablet production

Multivariate projection methods, such as principal component analysis (PCA) and partial least square (PLS) regression, are combined with DoE in formulation or process development for screening of a large number of influence parameters (fractionated factorial design) and further optimization of the important parameters, to study their interactions and possible non-linear behaviour (central composite design, Box Behnken, D-optimal, mixture designs).

3. PCA in exploring new molecular entities

QSAR and QSPR respectively (quantitative structure activity/property relationship) interlink biological effects or physical properties to the molecular structure of the respective substance. The best known example is the design and synthesis of new drug molecular entities in medicinal chemistry where the aim is that the drug molecule (API) interacts with the molecular structures at the site of action (e.g. receptors, enzymes). Another important step for a drug substance to act as a useful remedy is the uptake of such molecules into the body, which is a prerequisite to reach the receptor – has led to systematic PCA based studies of structure permeability relationships (e.g. intestinal barriers for the uptaker of oral drugs, or transport through the blood brain barrier; BBB partitioning).

Similar PCA methods have also been applied in formulation development by means of calculated quantum chemical descriptors for excipients (see Section 4.1.1.).

4. PCA in formulation development and processing

For the development of the formulation (composition) and the process (handling), all the experimental parameters during the entire manufacturing (such as chemical composition, processing steps, and processing conditions) contribute to the properties of the final product. In the following, examples of recent studies are briefly discussed, organized according to separate steps, although the entire flow of processing steps affects the product properties.

4.1 Excipient choice

As a rule, excipients have multiple functionality depending on the types of (other) materials present in the formulation, composition of the blends, and processes used. Well-known examples are filler-binders and lubricant-glidants.

A set of basic studies including four groups of excipients (filler, binder, disintegrant, lubricant) with several examples for each, in total almost one hundred excipients, were screened with respect to tablet properties (good mechanical strength and short disintegration time) (Gabrielsson et al., 2000; 2004). DoE combined with PCA and PLS were used in screening and optimisation: PCA provides a general overview over relationships and PLS models quantify the relationships between excipient properties and responses (tablet properties). Such mapping of excipients can be useful for selection of the appropriate material for a new formulation.

4.1.1 Examples of functional polymers as excipients

Microcrystalline cellulose (MCC) is a frequently used excipient with filler/binder function. It is derived from native cellulose through hydrolysis and purification. Using DoE and stepwise multiple regression analysis, particle properties and the functionality of different MCC products can be quantitatively related to the hydrolysis conditions (Wu et al., 2001).

As another example the formulation of pectin pelletisation masses using different granulation liquids is shown in the form of a PCA score plot mapping the experimental area. Correlation between properties of the masses and the respective additives was found

using quantum chemical molecular descriptors (QSAR) of the additives. Partial least square regression methods, mainly PLS-2 models, were used to quantify the effects (Tho et al., 2002). Based on the models, a rational choice of the composition of the formulation can be made.

4.2 Mixing / blending

Homogeneous powder blends are a prerequisite of the predefined dose of API per tablet. In optimized blending processes, homogeneity of the bulk is achieved.

However, segregation tendencies – becoming significant even for initially homogeneous bulk powder blends when these materials are transported - are even more important to consider. The effect of powder properties on segregation was studied, and PCA models developed to connect material properties to segregation tendency. A comparison of the multivariate approach and univariate approaches reveals that the latter leads to incomplete models (Xie et al., (2008)).

4.3 Particle size and powder flow

Multivariate latent variable methods have also been applied to mixture modelling of pharmaceutical powders. Particle size distribution was shown to predict powder flow (Mullarney and Leyva, 2009). Particle size distribution along with particle shape information has also been used to predict bulk packing and flow behavior (Sandler & Wilson, 2010).

4.4 Granulation

Wet granulation is classically done in high shear mixers or in fluidized bed equipment, or in a recent approach as a continuous process.

A basic investigation of general interest into the fluid bed granulation process is described by Dias and Pinto (2002), who used DoE and cluster analysis to find the relevant processing parameters and relations to product properties.

Another basic study of the fluid bed granulation process is described by Otsaka et al. (2011). PCA was first used to describe the relationships between a set of granule properties and to identify the properties that produce optimum tablet properties. In a second step, regression modelling was used to optimize the granulation conditions.

For wet granulation in high shear mixers, there are two different possibilities: The first one is a separate wet massing step and subsequent drying in another machine. The alternative is a single-pot set-up, where the drying step can be conducted in the same piece of equipment. Giry et al. compare these two processes (Giry et al., 2009) with respect to product properties using a set of formulations. This is a typical DoE and PCA application. Both processes led to products with only slight differences in properties. However, the robustness of the processes was different.

An alternative to wet granulation methods is dry granulation, basically by compression of dry powder blends to make granules. A dry granulation process conditions was studied within a PLS framework to predict selected granulation properties (Soh et al. 2008).

4.5 Drying

In-line monitoring of the water content is essential in order to find the end point of the drying step for optimum water content of granules. NIR (near infrared) spectroscopy is particularly sensitive to water content, and using PCA/PLS models enable prediction of the actual water content. In addition, the NIR spectra are also sensitive to other granule properties such as particle size. However, in bulk material of a wide particle size, the actual water content of the granules varies significantly with size. Nieuwmeyer et al. (2007) developed a method for characterization of both water content and granule size during fluid bed drying based on NIR spectroscopy.

4.6 Final blend; lubrication

The final blend is typically produced by blending solid lubricant into the granules. The problem with too long mixing times (“overmixing”) is that lubricant particles scale off and cover too much of the granule surface, which leads to weak tablets. As an example to monitor the blending profile (the degree of lubricant coverage) over time, and correlate this to tablet hardness, NIR was used (Otsuka & Yamane, 2006). Principal component regression was employed to model and predict the hardness of the tablets.

4.7 Tablet compression

Compression of the materials into tablets is a complex processing step, which is not yet fully understood. Amongst others, influences of particle size, shape, and structure on the deformation mechanism are difficult to separate and quantify. It has been shown that it is possible to derive basic material deformation characteristics during the compression step from in-line processing data using model materials (Klevan et al., 2010). Due to the complexity of the deformation of powder beds and the large number of parameters that may be regarded, screening of such in-line derived parameters for the most useful set of parameters is necessary in order to avoid over-determined functions (Andersen et al., 2006). Examples are discussed using a set of commonly used excipients of most diverse properties within the useful materials (Haware et al., 2009a; Roopwani & Buckner, 2011). The effect of particle engineering with regard to the tablet properties, such as tablet tensile strength, studied by PLS models (Otsuka & Yamane, 2006; Haware et al., 2010) using cross validation (jack-knifing). Prediction of tablet mechanical properties using PLS model can be made from NIR spectra of the blends (Otsuka & Yamane, 2009) or from in-line compression parameters derived on examples of very similar properties (Haware et al., 2009b).

Figure 4 shows a PCA biplot as an example how particle properties of different commercially available lactose qualities spread out in a design space. The data together with in-line compression parameters were used to predict the mechanical strength of tablets made with different blending ratios (formulations) and under different experimental conditions of compression (Haware et al., 2009b).

4.8 Combination of processes

Polizzi and García-Munoz (2011) proposes a quantitative approach to simultaneously predict mechanical properties of particles, powders, and compacts of a pharmaceutical

blend, based on the raw materials. They used a two-step, multivariate modeling approach created using historical physical data of APIs, excipients, and multi-component blends. The physical properties for each individual component were first transformed using a PCA technique to place them in a multivariate design space and capture property correlations. The scores from these PCA models were then weighted by the blending ratios prior to PLS regression versus actual measured blend properties. This method produced a complete prediction of all the material properties simultaneously which was shown to be superior to the prediction performance observed when applying linear ideal-mixing.

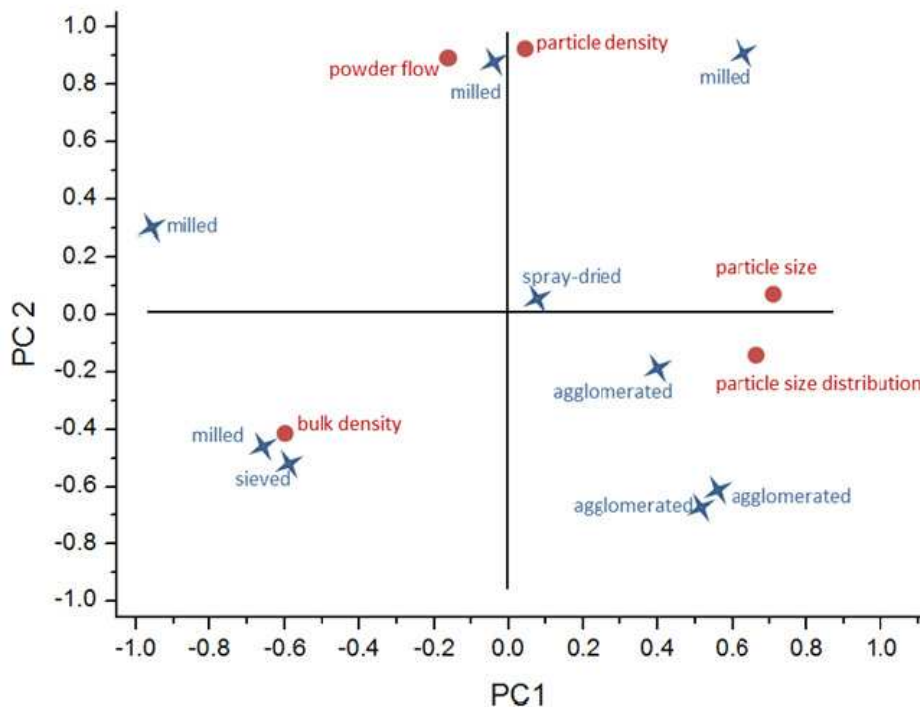


Fig. 4. Example of a PCA biplot showing powder characteristics of commercially available lactose grades spread out in the design space (modified after Haware et al. 2009b).

5. PCA in quality assurance of tablets

5.1 Spectroscopic methods

Molecular vibrational spectroscopy techniques, such as infrared (IR), near infrared (NIR) and Raman, are characterisation methods that have been applied to monitor both physical and chemical phenomena occurring during the processing as well as for off-line characterisation of raw materials and end-products. These techniques produce data of high dimensionality, since each sample is described with hundreds or even thousands of variables (wavelengths). Multivariate projection techniques, such as PCA are frequently combined with spectroscopic methods to enable detection of multivariate relationships

between different variables such as raw materials, process conditions, and end products. Also well-known spectroscopic methods that are easier to interpret, e.g. UV (ultraviolet) spectroscopy and X-Ray diffraction, have been suggested to benefit from the use of PCA.

Both NIR and Raman spectroscopic measurements can be done in a very fast (within seconds) and non-destructive way, making them suitable tools for real-time process monitoring. They are frequently used for in-line monitoring of processes, e.g. particle size growing during granulation or the water content in the granule (Räsänen & Sandler, 2007; Rantanen 2007). NIR is also used for monitoring the final quality of the single tablets, because it is possible to quantify the active ingredient in a non-destructive manner (Tabasi et al., 2008), and can be applied to identify counterfeit drugs (Rodionova et al., 2005). Another example is the prediction of tablet hardness based on NIR spectra of powders with lubricants (Otsuka & Yamane, 2006, 2009). For further applications of vibrational spectroscopy and chemometric methods in pharmaceutical processes, the reader is referred to the reviews by Gendrin et al. (2008), De Beer et al. (2011) and Rajalahti & Kvalheim (2011).

5.2 PCA in drug release

Sande and Dyrstad (2002) used PCA/PCR for parameterisation of kinetic drug release profiles, and showed that the combination of PCA and SIMCA was useful for classification of formulation variables based on the entire profiles. Also multi-way principal component analysis (MPCA) has been used to study entire tablet dissolution profiles and detection of shifts upon accelerated stability (Huang et al., 2011). Korhonen et al. (2005) calculated physicochemical descriptors (using VolSurf software) of different model drugs and correlated those to the respective dissolution profiles from matrix tablets. Again, the entire dissolution profiles without any parametric curve fitting were used in the models. This is a great advantage, since the contribution of different variables tends to change in the course of the drug release event due to the dynamic nature of drug release from the matrix tablets.

Another example of the non-parametric curve description of drug release from a sustained release matrix is the approach suggested by Kikuchi and Takayama (2010). They use non-parametric descriptors and non-parametric differences between release curves for optimization (24 h linear release) and prediction. Surface plots are used for prediction of composition of the matrix tablets.

6. Monitoring and sensors

Combination of instrumentation and multivariate analysis provides powerful tools for effective process monitoring and control enabling detection of multivariate relationships between different variables such as raw materials, process conditions, and end products. Multivariate methods play an important role in process understanding, multivariate statistical process control, default detection and diagnosis, process control and process scale-up.

Continuous monitoring of process parameters allows continuous regulation and adjustment. Given rational development of the parameters as a background, a statistical process control is possible in order to control the variation in a process within specification limits.

Furthermore, non-statistical variation caused by a specific event can be identified and the special causes thereof studied, with a possibility to eliminate these for the future.

In the case of tableting, continuous monitoring of the maximum compression force for each single tablet has been a standard in industrial production for more than 30 years. The force values are used as a measure for the individual tablet mass (and given homogeneity of the tableting material, also the dosing of each tablet). It is possible to sort out single bad tablets from the production line. A feedback loop needs to readjust the correlation between force and dosing based on sample analysis. By this, each tablet is held within the specification limits. Further development on tablet machine instrumentation includes measuring forces and displacements at different machine parts, and acoustic sensors in order to catch effects connected to lubrication problems.

Statistical Process Control (SPS) is the best way to take advantage of real-time monitoring. Based on the experience from process development, upper and lower warning and control limits can be set, where predefined action is taken: further trend analysis, actual changing of parameters, searching for the cause of an outlier. Figure 5 illustrates how SPS may be implemented in process monitoring. Trending analysis and feedback loops are necessary features to readjust these limits if necessary. In cases where secondary measures are used, reassuring the calibration with other measures is frequently conducted on a regular basis. A typical example is the relationship between compression force and mass of tablets. This is directly connected to the bulk density of the tableting material, which may change during the course of the actual tableting process. In many cases increased density is observed over time due to bulk material transport in the machine combined with machine vibrations. The mass of the tablets therefore needs to actually be checked on a balance.

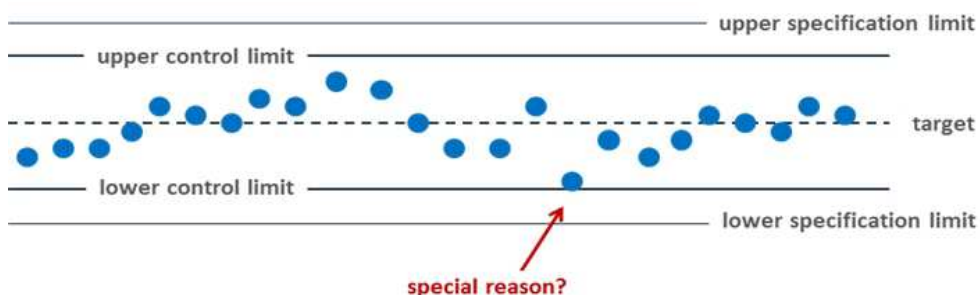


Fig. 5. Principles of Statistical Process Control (SPS) based on process parameter monitoring

Frequently used sensors based on NIR or Raman spectroscopy identify the chemical or physical variation between intermediates and products, particularly in the case of large numbers of samples:

- particle size distribution of powders and granules,
- granulation process monitoring,
- powder mixing optimization,
- scale-up of powder mixing,
- tablet properties (e.g. drug content).

These methods can be used to collect all batch characteristics, model all batches, detect outliers, and check future batches against historic batch models (in-line monitoring). These are prerequisites to diagnose out-of-limit-batches.

7. Future of tablet manufacture development

Traditionally, pharmaceutical manufactures are batch-based production methods with sample-based end-product control. This includes a sampling procedure with all its drawbacks. The future will be in the real-time in-line monitoring during processing, in order to be able to control the processing steps rather than end-point controls on the product. This will consequently lead to continuous production processes, which can be conducted in equilibrium. Continuous granulation has been developed already for a number of processes, including fluid-bed granulation, extrusion, and roller-compaction. These days, complete continuous production lines from the powder to the tablet are being introduced to the market.

The vision is to have such continuous production all the way from API synthesis to the final drug product ready for the market. The advantage will be a controlled and stable process with less product variation compared to traditional batch-based production methods. Furthermore, sample-based post-production quality control will be unnecessary and discarding or reworking of bad batches will not happen again. The real-time-release of the product will also become possible.

8. Conclusion

Although pharmaceutical tablets have been produced for more than 100 years on an industrial scale, there are up to day a number of unresolved challenges in tablet development, manufacturing and quality assurance. The basic factors that influence the product properties are widely known. However, depending on the individual composition of the tablet, numerous factors may have different impact on product quality. Furthermore, there is commonly a large interaction between many of these factors. Depending on composition, processing conditions for the different steps and environmental conditions the properties of the final bulk material (tableting blend) can differ widely. The actual tablet compression step, again committed to numerous processing factors, in addition would have large impact on the product quality. These complex relationships open a multivariate perspective and require suitable statistical methods.

For the tableting procedure, the steps that have been studied include powder blending, granulation, particle equalisation, lubrication, compression, coating, and drug release studies. Such step-wise studies have brought light into the impact of the parameters and their interactions and increased the understanding of the respective processes.

Pharmaceutical products underlie special requirements for their quality set by the health authorities. Therefore, the pharmaceutical development has been one of the first areas where factorial analysis and PCA/PLS have even become compulsory.

Moreover, the requirements for pharmaceutical drug products are under ongoing revision. It is a general trend that the requirements set higher standards with each new revision in order to assure safety and efficacy of the products. Some of the most important recent

developments are the introduction of “Quality by Design” and PAT. It is a prerequisite to understand the processes, factors and interactions for the entire production line. Figure 6 depicts how the statistical tools are related to each other, and used interconnected in tablet development, manufacture and quality assurance.

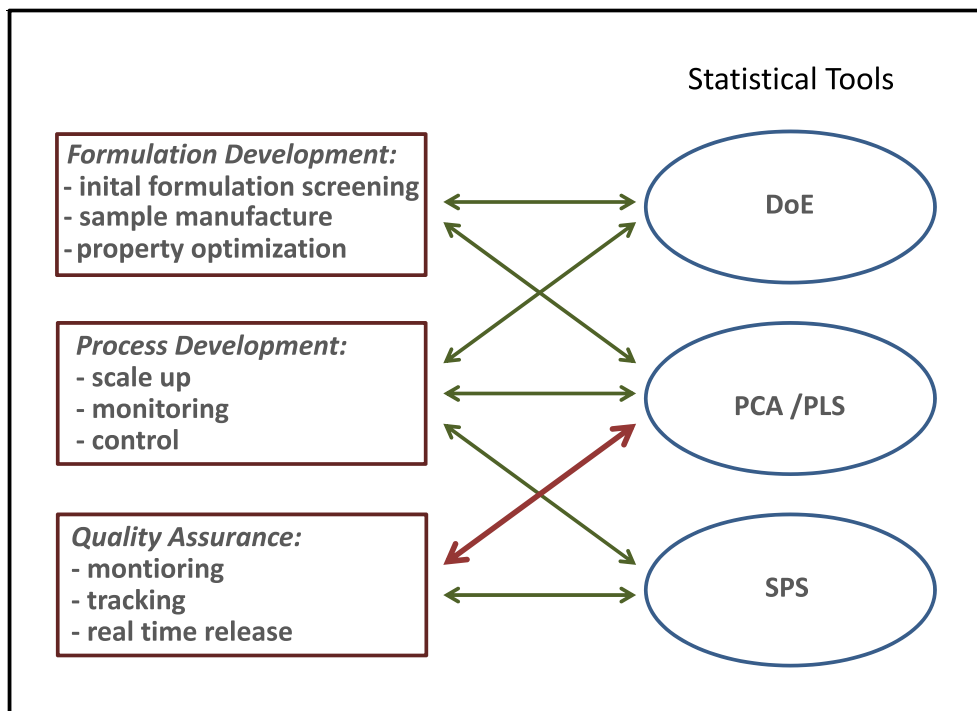


Fig. 6. A schematic overview of which statistical tools mainly are used in tablet development, manufacture and quality assurance

The development in the regulatory guidelines combined with new technology has found its expression in the efforts towards continuous production of pharmaceutical products, and in the forefront thereof the tablet manufacture due to both its relevance and complexity.

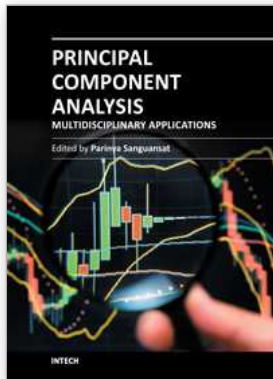
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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Phone: +86-21-62489820
Fax: +86-21-62489821

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