PAT and beyond
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to the inverse sensitivity indicator and the error indicator and was superior in both cases.

CHAPTER 3. SOLID DOSAGE FORM MANUFACTURING

Solid dosage forms (SDF) manufacturing is the production of tablets and capsules. When the formulation scientist is starting to develop a new dosage form, SDF is the first option to consider. Some of the advantages with SDF are\textsuperscript{27}:

- High accuracy of API dosage
- Few problems with drug stability compared to other drug types
- Mass production is economic compared to other drug types
- The final drugs are easy to pack and distribute to customers
- Little inconvenience for the patients when using the drug

A tablet in its most simple form is a mixture of API and supporting excipients which is compressed into a tablet. In most cases the API and excipients are crystalline powders. These compounds can in some cases just be mixed and compressed directly into a tablet (direct compression). In cases where that is not possible, they are blended with some kind of adhesive liquid (granulation fluid) to form granules (wet granulation) which adds technical qualities to the formulation e.g. flowability, homogeneity and compressibility. The wet granules are dried, mixed with other compounds that prevent the granules from sticking in the tablet press and finally the granules are compressed into tablets.

When the tablet is administrated into the body it disintegrates and breaks down first into granules and then primary particles. From the granules and primary particles the API is dissolved (called dissolution) and is being absorbed into the blood stream and transported to the intended parts of the body. Another SDF is a capsule. The excipients and API are placed in a gelatine capsule either in the form of a powder mixture or granules. The gelatine capsule dissolves when administrated in the body and dissolution from the granules and primary particles
takes place. Because there are no capsule based drugs currently in Novo portfolio or research pipeline, all work in this thesis has been focused on tablet based drugs. This however does not mean that this research cannot improve capsule manufacturing, as it is only the last physical form that differ capsules and tablets. Until the point where the tablets are compressed or the capsules filled, the manufacturing processes are similar.

Manufacturing processes and quality control
In this paper the different manufacturing processes and quality control will be explained in more detail. Quality control is divided into in-process quality control which is control performed during processing and final quality control, which concerns the final drug product. Especially the use of NIR as a quality control tool will be dealt with. In Table 3 is a list of terms that explain how the sample is presented to NIR analysis. These terms are commonly used in the literature and this thesis.
Table 3. Overview of measurement modes in NIR spectroscopy.

<table>
<thead>
<tr>
<th>Mode</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off-line</td>
<td>The sample is removed from the process and send to NIR analysis in a laboratory.</td>
</tr>
<tr>
<td>At-line</td>
<td>The sample is removed from the process and analyzed with NIR on an instrument placed in close proximity to the process.</td>
</tr>
<tr>
<td>On-line</td>
<td>The sample is automatically removed from the process e.g. a flow stream, and measured in the NIR instrument and returned to the process or discarded.</td>
</tr>
<tr>
<td>In-line</td>
<td>A fibre optic probe or optical window is interfaced between the NIR instrument and the process.</td>
</tr>
</tbody>
</table>

The two most common solid dosage forms manufacturing processes are direct compression and wet granulation (Figure 6). Both these processes are used at Novo and a lot of research has been performed on these\textsuperscript{28-30}. Both types of processes have been investigated in this project. Figure 6 depicts direct compression and wet granulation. Each of the processes consists of several unit operations which will be described hereafter.

![Diagram of manufacturing processes](image)

Figure 6. Schematic overview of the two major manufacturing routes for tablets. Direct compression (top) and wet granulation (low).
API SYNTHESIS

For both process types the starting point is the manufacturing of the active pharmaceutical ingredient (API). This is usually done by chemical synthesis followed by crystallization, drying and milling. The synthesis process is in many cases run according to a recipe with some form of monitoring e.g. temperature, pH and conductivity etc. but little or no process control. Without process control, the API yield and quality are likely to vary because of variation in the raw materials, environment and equipment. The traditional monitoring tools provide a thermodynamically process view and can be used for process control, but the introduction of process analyzers adds more chemical information about the synthesis process. Raman spectroscopy has proven feasible for monitoring synthesis processes\(^{31}\). Also infrared spectroscopy has proven successful for synthesis monitoring\(^{32,33}\). FT-IR provides high quality spectra which are easy to interpret and equipped with ATR crystal probes many different complex samples e.g. liquids with suspended crystals can be measured. But IR has a few drawbacks. Some FT-IR instruments require nitrogen cooling which makes them stationary. Secondly, the probe is connected to the instrument with a mechanical arm wherein the IR beam is transported, using optical mirrors in the joints of the arm. A NIR probe has an advantage over a FT-IR probe because it is connected to the instrument with fibre optics which can bend and transport NIR light over a long distance. This provides some operational benefits in a synthesis plant, because the instrument can be apart from the synthesis unit in a protected room and the instrument does not require cooling. NIR probes can be inserted directly into the reaction vessel and depending on the optical properties of the solution reflectance, transmittance or trans-reflectance probes can be used. Stordrange et al.\(^{34}\) demonstrated how a reactant and intermediate component could be monitored with a NIR trans-reflectance probe during the chemical reaction. An alternative to using a probe is to pump the sample out of the reaction vessel for analysis. Blanco et al.\(^{35}\) demonstrated an on-line setup where a sample flow was pumped from the reactor through a flowcell in the NIR instrument and back to the reactor.
After synthesis, the API is in most cases removed from the solution with a crystallization step. Crystallization can be a difficult process to control, and if the API can have several polymorphic forms, this process step can cause big quality problems. The polymorphic form can have a significant influence on solubility and the biological efficiency of the final drug. In other cases the level of impurities or the particle morphology and size are mainly depending on the crystallization process. In the recent years more analyzers are used for monitoring and control of crystallization processes. On of the most promising techniques is a focused beam reflectance measurement (FBRM) with a probe directly in the crystallization slurry. A laser beam is sent into the slurry of liquid and particles through a lens rotating at high velocity e.g. 4500 rpm. The beam is focused in a point in front of the probe window and when the beam hits a particle the instruments detects the backscattered light. Depending on the size of the particle the duration of backscattered light will vary and the average chord length of the crystal can be calculated. The technique has proven rugged, precise and easy to install and will presumably be one of the most widely used and successful PAT tools. But FBRM is only providing physical information about the crystals. Spectroscopic measurements on the contrary can provide both physical and chemical information. Most of the applications in the literature are based on MIR or Raman analyzers, but NIR based solutions have also been reported. Févotte et al. for example used a NIR reflectance probe to monitor polymorphic transition of an API in suspension and also later during filtering of the crystals from the suspension. Vaccari et al. showed how a crystallization process could be monitored and controlled by NIR. The FDA actually participated in an excellent white paper on PAT and crystallization processes.

**Direct compression process**

Direct compression is a tablet manufacturing process with few process steps. The API is mixed with excipients and the formulation is poured directly into the tablet machine and compressed. After tableting the tablets are film coated and
finally packed (Figure 6). It is a practical and economic advantageous process type which can be performed with a minimum requirement for production facilities and equipment. For APIs that are sensitive to heat and moist, the process does also provide better stability then wet granulation processes where contact with moisture and drying steps are required. Key for the direct compression is that mixtures have good flowability and good compression properties.

**Mixing**

After the materials are weighed they are poured into a mixer and mixed according to a predefined time interval. The most critical quality aspect of the powder mixing processes is to ensure blend uniformity. When the final tablets are compressed each tablet should contain the same amount of API. If the prior mixing is not performed optimally the API is not homogeneously spread in the powder blend and large variation in the API content of the final tablets will be likely to appear. The in-process quality control of blend uniformity is traditionally done by removing a small set of powder samples from the blend. The samples are analyzed in distant laboratories using time consuming methods. This means that the analysis results are first available days/weeks after the entire manufacturing has ended, leaving no opportunity for improving the blend quality.

A great deal of the demonstrated NIR applications in SDF has actually been monitoring and control of blend uniformity. Popo et al.\(^45\) demonstrated how powder samples could be removed from the mixing process and the API content quantified. Ufret et al.\(^46\) measured the powder mixing process though a glass window in the mixer and evaluated the mixing process in real-time. Hailey et al.\(^47\) developed an automated system where a NIR probe was inserted through the bearings of a V-blender for end-point control of the mixing process.

On of the key differences between the suggested NIR methods is sampling. In some methods the NIR measurements are always performed at the same spot in the mixer over time\(^48\). The problem is that the spectra lack spatial information about overall homogeneity and "dead spots" cannot be detected. Other examples
include the mounting of six optical windows on the surface of the blender from where the monitoring is performed\textsuperscript{49}. With this approach information is only gathered from the surface regions of the blender.

In this project a novel method was developed, using a NIR probe and control charts to monitor the quality of mixing\textsuperscript{5}. A hand held NIR probe was inserted at various positions in the mixer at different time points during mixing. Different model types were developed to predict the API concentration in each measurement spot. The variance and mean of the API concentration predictions, were compared statistically to a "golden batch" (batch with perfect mixing) in two control charts. One control chart for the variance and one control chart for the mean. The 'golden batch' was used to set the control limits in the two charts. With this method a mixing process was investigated. At different time points the mixer was stopped and fifty spectra were recorded. The variance and mean of the fifty API predictions were calculated and plotted in the two control charts. The optimal blend uniformity was achieved after 25 minutes and after that the mixing quality worsened. This is called segregation or de-mixing and usually these phenomena are known to exist but difficult to identify using traditional blend uniformity analysis. After thirty minutes of mixing, the variance exceeded the limits in the control charts (Figure 7). This was indicating that the homogeneity (expressed as analyte variance) was getting worse i.e. higher compared to the golden batch. In a real life application the operator would terminate the mixing process when the limits are exceeded and not continue de-mixing as the example illustrates.
Figure 7. The de-mixing phenomenon was detected after thirty minutes of mixing\(^4\). At time points where the variance was different from the golden batch the mean could not be compared statistically to the golden batch (marked with x in mean chart).

The method offers several advantages over other NIR methods. It was flexible in the way that it could be used as a qualitative method, and also as a quantitative method with a few extra calibration batches. The control charts were based on F and T statistics and finally the sampling procedure is comparable to common industry practice. This allows a full characterization of the blend quality in all parts of the mixer. The method is simple and a strong tool for performing in-process quality control of the mixing process. The analysis is applied at-line and only takes minutes. With the method, blend uniformity can be assured before the powder blend is compressed into tablets.

**TABLETTING**

The compressed tablet is subjected to a series of quality tests e.g. hardness, water content, dissolution, disintegration time, microbiology test, quantification of impurities and content uniformity tests\(^{27}\). Many of these tests are time consuming, are performed in distant quality control laboratories and only a few
number of samples are analyzed which in return provides weak statistical certainty of the entire batch quality. Also for quality control of whole tablets NIR has been proven successful. Chen et al.\textsuperscript{50} demonstrated how both the API content and also the hardness could be quantified with NIR. In a recent work by Donoso et al.\textsuperscript{51} even the tablet porosity could be quantified using reflectance NIR.

Tablets can be measured both in reflectance\textsuperscript{52} and transmission mode\textsuperscript{53}. When measuring in reflectance mode the whole NIR spectrum is available but when using transmission spectroscopy usually only the second and third overtone region is successfully measured. The reason is that the penetration depth of NIR radiation decreases when moving from higher to lower wavenumber i.e. the absorption increases. This is also the reason why reflectance spectra is showing an upward moving curvature, when going from higher to lower wavenumbers. In many cases it is not a problem for transmission spectroscopy of tablets to only use the 2\textsuperscript{nd} and 3\textsuperscript{rd} overtones as the molecular information is present in the entire NIR region. Figure 8 shows the reflectance spectrum of a tablet and the transmittance spectrum of the same tablet. In the transmittance spectrum the region from 7000 cm\textsuperscript{-1} to 4000 cm\textsuperscript{-1} is not useful because of complete absorption. Also the absorption values below 7000 cm\textsuperscript{-1} are high and only 10 % to 0.1 % of the light exits the tablet, nevertheless this is sufficient to make a good calibration model.
Figure 8. Reflectance spectrum of tablet (top) and transmittance of the same tablet (bottom).

One of the advantages with NIR is that no sample preparation is needed and the measurement is non-destructive. This also means that everything that has NIR absorption in the sample matrix, contributes to the final spectrum. In normal quantitative calibration the objective is to correlate the spectral variance to one particular analyte or property of interest disregarding the information of the other components in the sample matrix.

In the project a new methodology was developed called net analyte signal based statistical quality control (NAS-SQC)\(^6\) where all components could be monitored simultaneously. The method was demonstrated with transmission NIR spectra measured on a commercial available anti-inflammatory solid dosage product (Feldene) produced by Pfizer, who kindly delivered data for the paper.

The measured spectral vector is the sum of the spectra of the analyte of interest, the excipients, and other physical phenomena (called interferents), this is
referred to as Beer’s law. With NAS-SQC, the idea is that the measured spectral vector is split into three independent vectors. One vector is called net analyte signal (NAS) vector and is unique for the analyte. The other vector is called interference (INT) vector and is unique for the excipients and the interferents. The NAS and INT vectors describe the systematic part of the spectroscopic variation. The last vector is describing the non-systematic or residual variation and this vector is called the residual (RES) vector. In Figure 9 is an example of a 1st derivative tablet transmission spectrum, which has been split up into the NAS, INT and RES vector.

![Image](image.png)

**Figure 9.** The spectral vector (NOC sample spectrum) is split into three vectors; NAS vector, INT vector and RES vector.

For each of the three vectors a separate control charts was developed with statistical limits. The control charts were developed with a set of good quality sample spectra. The samples should be having the analyte concentration and the composition of the interferents within a desired range. These in-control samples are named normal operating condition (NOC) samples. The NOC spectra are
split into the NAS, INT and RES vector parts and for each part statistical limits are calculated for their respective control charts. The control charts are called NAS, INT and RES chart. In the corresponding paper\(^5\) we also demonstrated how the limits in the NAS chart could be either statistical limits or concentration limits depending on the user requirements. When the control charts were developed, future samples could then be monitored. In Figure 10 are examples of fifty four 'future' samples. For the NAS chart concentration limits were calculated and the two horizontal lines equal the range 85\% to 115\% (desired range) of the target analyte content in the tablets. The samples symbolized with plus-signs were somehow out-of-control and the samples symbolized with squares were in-control samples. Samples # 1-10 had API content slightly below 85\% and these samples were below the lower NAS control limit. Samples # 11-20 had API content above 115\% and were above the upper NAS control limit. Samples # 21-22 were special samples with API within the desired range but elevated moisture content; these samples were flagged in the INT chart but within the limits in the NAS chart. Samples # 23-34 were special samples where the composition of the interferents were out of the desired range while the analyte was within the desired range; these samples were also flagged in the INT chart and within the control limits of the NAS chart except for samples # 23-25, but some explanations for that unexpected result was given. Finally, samples # 35-44 were NOC production samples within the desired ranges and samples # 45-54 contained analyte slightly below the upper NAS control limit, but still in-control. This is clearly represented by the specific charts. Some of the residuals for samples # 45-54 were also slight above the limit in the RES chart. An explanation could be that these were special laboratory samples that with a sample composition that was deliberate different from production samples that were used to develop the chart limits. These differences might account for the high residual values.
Figure 10. The validation samples plotted in the NAS-SQC control charts\(^5\). The samples out-of-control is symbolized with plus-signs and the samples in-control is symbolized with squares.

The NAS-SQC method provides some new and improved possibilities of ensuring multiple quality characteristics. Also diagnostics is improved which makes trouble shooting easier in case of out-of-control situations.

**COATING**

After tableting, a film coating is often applied to the tablets. The film coating is sprayed upon the tablets in either larger drum or pan coaters or the coating is performed in a fluidized bed system. The purpose of the film coating is to e.g. add mechanical strength, colour, improve taste or protect the API from degradation imposed by moisture or oxygen. The amount of coating applied to the tablets are usual not determined despite it in some cases is influencing the final drug product quality. Andersson et al.\(^55\) showed how the coating could be determined with reflectance NIR both on single tablets and also in-line during coating\(^56\).
PACKAGING
After coating the tablets are packed. In multi-product facilities or during manufacturing of placebo and tablets with API for clinical trials, it is of vital importance that the different tablets are not mixed together. Also here NIR has been useful, because the measurement can be performed non-destructively through the packaging material and the tablets can be identified, even in-line as the packed tablet pass on a conveyor belt\textsuperscript{57-59}.

Wet granulation process
In case of a cohesive API or a formulation with poor flowability wet granulation can be advantages. After mixing of the API and excipients a granulation liquid is mixed into the powders and larger granules are built. The granulation liquid is typically a mixture of a binder and water.

GRANULATION
Granulation is typically performed in a high shear mixer or a fluid bed reactor\textsuperscript{29}. In fluid bed granulation, the powder mix is fluidized by a flow of air injected upwards through the bottom of the reactor. The granulation liquid is dispersed from a spraying unit above the powder bed. When granulation is finished the air flow is kept and the granules dried in the fluid bed reactor. In high-shear granulation, an impeller maintains the powder in agitation in a closed vessel, and here also a granulation liquid is sprayed from the top. As the granulation liquid droplets disperse in the powder, granulation starts. During granulation, another smaller wing (chopper), mounted in the side of the vessel, rotates thereby reducing larger agglomerates. When the granulation is finished, the granules are in most cases moved to another process unit and dried. Usually the granulation process is simply controlled by time and no or few in-process measurements are used in order to obtain consistent high quality granules. This, in spite that many properties of the granules and final drug are controlled by granulation variables\textsuperscript{60-62}.  

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Some in-process measurements have been used e.g. power consumption has been demonstrated as a useful monitoring tool and also torque measurements. Also some more sophisticated examples of process monitoring and control of the granulation process have appeared. Watano et al. demonstrated a very sophisticated setup. With an image probe inserted in a high shear mixer they recorded images of the granules with a CCD camera. The images were applied to a model and used for an automated feed back control and control of granule growth. Another emerging technique in pharmaceutical industry is acoustic sensing that can be used to monitor boiling processes, gas evolution, mixing, grinding and fluidization processes. If the material has density and compressibility changes during the processing the sound velocity through the material will also change, which can be measured with piezoelectric acoustic emission sensors somewhere on the process vessel. The recorded power spectra can then be used to provide a process 'fingerprint'. Whitaker et al. demonstrated end-point monitoring of a granulation process with acoustic monitoring and PLS prediction of future tablet crushing strength with the acoustic data measured during granulation. One of the advantages with acoustic monitoring is that it is a truly non-invasive technique, not very expensive and easy to install. The sensors are literally glued onto the process equipment. Some drawbacks are that the power spectra are difficult or impossible to interpret. Secondly it will be difficult to transfer a model to another process unit as the 'sound' of the individual process equipment is part of the model data. Acoustic monitoring is still in its infancy in the pharmaceutical industry but is has some appealing advantages and might become a popular technique after maturation.

Because NIR measurements are affected by both physical and chemical properties of the granule sample it is very useful for monitoring granulation. Otsuka et al. measured granules from wet granulation with reflectance NIR probe and made calibration models between NIR spectra and median particle size of the final granules. Also fluid bed granulation has been monitored with NIR.
Rantanen et al.\textsuperscript{68} demonstrated how the moisture content could be monitored in real-time during granulation and drying in a fluid bed reactor using in-line NIR measurements with a reflectance probe. In another paper by Rantanen et al.\textsuperscript{69} in-line NIR was used to define end-points for different phases in a fluid bed granulation process.

In this project a tablet manufacturing process was examined including high shear granulation. Using a hand-held NIR probe directly into the high-shear granulator unit, batches with particle size quality defects were identified. The results are presented in detail at page 45 in this thesis.

**Drying**

Wet granulation is followed by drying of the wet mass granules. If the preceding granulation has been performed in a fluid bed reactor the drying is simply continued in the fluid bed reactor by fluidization of the wet granules with hot air. When granulation has been performed in e.g. high shear granulators the wet granules are dried in other process equipment e.g. fluid bed reactor. Alternatively some high shear mixers have build-in drying capability based on microwaves.

During drying a series of complex physical and chemical processes take place within the granules. Evaporation of water from the surface is taking place; water is diffusing from the core of the granules to the surface and solidification of crystal bridges within the granules. If the drying is performed in a fluid bed there is also destruction of larger agglomerates by shear forces when the particles are fluidized. Water has a large contribution in the MIR and NIR spectral region and can easily be monitored during the drying process with these techniques. With NIR it is also possible to discriminate between the different states water can be e.g. free water and crystal water\textsuperscript{70}. Dziki et al.\textsuperscript{71} showed how NIR could be used to discriminate between acceptable and unacceptable batches of sarafloxacin for formulation purposes based on the evaluation of water mobility within the crystal lattice.
Multiple phenomena are on-going during drying and distinct drying phases appear over the entire period of drying. Therefore, in-line NIR monitoring is a valuable tool in order to monitor, understand and apply process control. A few papers have described in-line drying monitoring in fluid bed reactors by NIR. Morris et al.\textsuperscript{72} measured NIR non-invasive through a lower positioned inspection window in the fluid bed reactor. This is an easy way to perform NIR monitoring but in the authors experience fouling of inspection windows happens frequently, which could blind the measurements. Frake et al.\textsuperscript{73} mounted a reflectance probe directly into the fluid bed reactor near the bottom of the reactor. The probe window was positioned near the reactor wall in the downward flow (to ensure the probe was kept clean), at a point of high product density. No detailed instructions of how to make the NIR probe port were provided.

It was decided to use the approach demonstrated by Frake et al.\textsuperscript{73} and a probe port and a customized reflectance probe were designed. Though it is fairly easy to install a NIR probe into a fluid bed reactor, a few design considerations need to be taken into consideration. Some of the main design considerations were:

- Prevent intrusion of air alongside the probe which can disturb material flow and the measurements in front of the probe
- Easy cleaning
- Removable probe and replaceable by plug
- Maintenance free optical probe window, with minimal risk of material fouling
- Adjustable penetration depth for the probe in order to optimize measurements
- Easy to perform background measurement with reflectance standard

The solution was a probe port in stainless steel and a probe adaptor with an inner cylinder in Teflon (Figure 11 and Figure 12). First the position of the probe
port was selected in close proximity to a sampling port so representative reference measurements could be taken. Also downward material flow and a high product density were present at that position which would improve the likelihood of good spectra. Secondly, this position in the mixer will always be covered with moving material regardless of the batch sizes that are practice in the Novo laboratory. By installing a Teflon cylinder in the adaptor, a tight fit was achieved and there was no air intrusion along the probe. The mounting screw could add pressure to the probe and maintain it in-position during operation and the penetration depth could vary and be optimized. It was discovered that a good measurement was obtained when the face of the probe was approximately 2 mm off the reactor wall. After the probe was fit in the adaptor, the adaptor was inserted into the NIR probe port until the mounting collars of the NIR probe port and the adaptor meet. The adaptor was locked to the NIR probe port with a standard wing screw (Figure 12). A metal plug with a collar and inner dimensions of the probe port was also manufactured which could replace the NIR probe when this was not in operation. The reflectance probe was custom build by Bruker Optics Scandinavia. A special electro polished optical window was used at the end of the probe and no material fouling was ever experienced, either in the granulation or in the drying process. Finally, if a reference measurement was needed before material was poured into the reactor, the adaptor with probe could easily be removed and a reference measurement could be performed. If this procedure was not remembered it was also possible to gently remove the NIR probe from the adaptor, perform the reference measurement and place the probe back into position in the adaptor, without wet material pouring out.

Figure 11. Cross section view of NIR probe port, adaptor and reflectance probe.
Figure 12. Picture of NIR reflectance probe and probe port in laboratory fluid bed reactor at Novo.

The probe interface was used for monitoring drying processes with in-line NIR in this thesis. At page 51 it is demonstrated how calibration models were built between in-line NIR reflectance spectra and loss-on-drying and drying curves were predicted for a set of DoE batches.

Tabletting, film coating and packaging are similar for granulated drugs and will not be further described.