A SPECIAL ADVERTISING SECTION

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Introduction

In the pharmaceutical industry, roller compaction is widely used, not only in smaller companies, but also in Big Pharma for OTC and prescription products, for generics and branded material. In fact, dry granulation by roller compaction is an established process in pharmaceutical formulation and production of manufacturing solid oral dosage forms.

A key challenge for solid oral dosage formulations are the specific properties of the API that needs to be transferred into a finished dosage form. Often, enabling technologies such as spray drying and hot melt extrusion are needed to transfer active ingredients into absorbable and easily soluble systems, particularly for BCS Class II and IV.

In general, for BCS Class I and II compounds, conventional technologies like granulation and layering can be applied. When wet granulation does produce satisfying results, roller compaction should be the technology of choice.

The goal of agglomeration technologies is to increase the particle size to modify the particle properties in a way that the particles are free-flowing, non-segregating, and suitable for compression. However, as seen in Figure 1, the different enabling technologies result in agglomerates with different morphology.

The left pictures shows granulates made by using solvents, the image on the right hand side represents roller compacted granules. Quite obvious is that roller-compacted material is rather dense, whilst fluid bed granulates are relatively fluffy. The other two solvent-based granulation technologies --the vertical and the agglomerative granulation-- result in systems with intermediate bulk densities.

Why Should Roller Compaction Be Used?

The process of roller compaction starts with the powder, which consists of fine, non-flowable material. An intermediate, called the ribbon, is made. By gently milling this ribbon, granules are obtained. This is the dry agglomeration process Figure 2.

A feed hopper with a stirring element for breaking powder bridges feeds material into a feed auger. This auger transfers the material into a tamping auger, which deposits the material in the nip area between the rolls. Then the material is processed at a given force, a given gap and a given speed of the rolls. The densified material is milled with a granulator system, of which the speed--the angle of rotation and the direction of rotation-- can be selected by the user. The force applied to the powder between the rolls is the most important parameter, followed by the gap. In general, speed has hardly any influence on the ribbon properties as long as it is smaller than 20 rpm.
These three parameters—force, gap, and speed—are the most relevant ones for roller compaction, because they are critical for the ribbon strength. Ribbon strength is uniquely related to the ribbon density, the so-called solid fraction.

**The Pros and Cons of Roller Compaction**

As ribbon density is the most important parameter in formulation development, you only need to investigate the influence of ribbon density on the tableting properties, dissolution rate, etc. This is typically done by performing experiments at four or five roll compaction forces at a given gap and roll speed. Figure 3 shows how efficient scale up in roller compaction can be performed. A scale up factor of 750 is absolutely no exception, when using the same machine like e.g. a Mini-Pactor®, by just increasing the run time and the roll speed.

Together with the effective development strategy (investigate the influence of ribbon density on granule properties), dry granulation is the technology, which enables a really fast time to market upon development.

Furthermore, dry granulation equipment saves quite a bit of floor space compared to using a combination of a high shear mixer and a fluid bed dryer with comparable production capacity. And, the investment cost for the equipment is less than the combination of a high shear mixer and a fluid bed dryer.

Another process cost saving is based on the reduction of the number of manufacturing steps compared to wet granulation as shown in Figure 4. Finally, the personal costs of roller compaction technology are low because the process is automatically controlled.

In addition, a roller compactor can easily be equipped with PAT tools for controlling ribbon density. This guarantees that you can run your batches in a reproducible way.

It is important to note that roller compaction has some drawbacks as well, as highlighted in Figure 5. First, you may end up with a high amount of fines (defined by having a size smaller than 90 microns), if you are not able to get an appropriately strong ribbon. And this may cause flowability problems. In general, the amount of fines can be reduced by...
increasing the ribbon density by increasing the force or decreasing the gap. Yet remember that at too large densities (e.g. at large forces), the compactability of the dry granulate might become too small for obtaining strong enough tablets. By selecting appropriate dry binders, the density resulting in strong enough ribbons for obtaining a flowable and recompactable granulate can be influenced markedly.

Key Parameters for selecting Excipients

Besides particle size distribution, morphology and structure are key influencers of dry binder properties. It is also important to be aware of the plasticity of the material. It is usually related to the glass transition temperature of the excipient.

When considering the chemical nature of products, there are two possibilities:

First is the group of the synthetic polymers, where we combine products derived from N-vinyl pyrrolidone (NVP). This is the group comprised of Copovidone and Crospovidones. The second group comprises some derivatives of natural polymers, mainly derivatives of cellulose or starch. The cellulose group comprises of microcrystalline cellulose and cellulose ethers, such as HPMC and HPC.

As mentioned earlier, particle size is a very important parameter. Thus these seven excipients have been grouped according to their particle size. The first group,

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**Figure 3. Scale Up Factor in Roller Compaction**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production time</td>
<td>x 75</td>
</tr>
<tr>
<td>Roll speed from 2.0 to 20 (30) rpm</td>
<td>x 10</td>
</tr>
<tr>
<td>Roll gap from e.g. 2.5 to 5 mm</td>
<td>(x 2)</td>
</tr>
<tr>
<td><strong>Total, with same machine:</strong></td>
<td>x 1500</td>
</tr>
<tr>
<td>Roll width from 2.5 to 10 cm</td>
<td>x 4</td>
</tr>
<tr>
<td><strong>Total, with same family of machines:</strong></td>
<td>x 6000</td>
</tr>
</tbody>
</table>

*With a Mini Factor, at 2 rpm and 2.5 mm gap, in 0.2 hrs ca. 1.0 to 1.2 kg would be made

**Figure 4. Process cost reduction because of less Solids Development Consult steps**

<table>
<thead>
<tr>
<th>Process cost estimate (£/kg)</th>
<th>Wet granulation</th>
<th>Roller Compaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Weighing of ingredients</td>
<td>0.40 – 1.00</td>
<td>0.40 – 1.00</td>
</tr>
<tr>
<td>2. Blending of ingredients</td>
<td>0.20 – 1.50</td>
<td>0.20 – 1.50</td>
</tr>
<tr>
<td>3. Prep. granulation fluid</td>
<td>0.50 – 0.75</td>
<td>0.20 – 1.50</td>
</tr>
<tr>
<td>4. Granulation</td>
<td>1.00 – 2.00</td>
<td>1.00 – 2.00</td>
</tr>
<tr>
<td>5. Wet sieving</td>
<td>0.30 – 0.70</td>
<td>(0.30 – 0.70)</td>
</tr>
<tr>
<td>6. Drying process</td>
<td>1.50 – 3.00</td>
<td>1.00 – 2.00</td>
</tr>
<tr>
<td>7. Dry sieving process</td>
<td>0.30 – 0.70</td>
<td>0.50 – 0.75</td>
</tr>
<tr>
<td>8. Add. of external phase</td>
<td>0.30 – 0.70</td>
<td></td>
</tr>
</tbody>
</table>

4.70 – 10.35 1.90 – 5.20

Cost reduction by at least a factor 2 to 2.5

Initial investment cost typical amortize quickly due to immense efficiency leap.


**Figure 5. Dry Granulation CONS**

**Cons**

- High amount of fines (<90 μm) possible
- Reduction of tensile strength of tablets (Initial investment into equipment)

called the ‘fine group’, contains the products with d50-values of less than 10μm. The remaining four examples have d50-values exceeding 50μm. **Figure 6**

**Formulation Examples**
Based on this data about concerning the seven excipients, two formulation examples are discussed. **Figure 7** shows a simple placebo formulation consisting of Dicalcium Phosphate and a dry-binder. The blend is roller compacted using a Gerteis Mini-Pactor® at gap density of 45% by adapting the roll compaction force. The obtained granules are compressed to tablets at compression forces of 10, 18, and 25kN.

The particle size distribution of the resulting roller compacted granules are shown in **Figure 8**. Here, fines are defined as particles smaller than 180μm. Two observations can be made. First, the Copovidone- and Crospovidone family shows lower fine concentration compared to celluloses. Second, the excipients of the ‘fine group’ result in the lowest percentage of fines in the granulated material.

The next parameter we review in this example is the disintegration time. It generally depends on the compression forces applied during tableting. Disintegration time of tablets manufactured from roller-compact ed material decreases for most of the formulations. A slight prolongation is only visible for Kollidon VA 64 grades when compressed at 25kN.
Slide 39 shows the results for the tablet hardness expressed as tensile strength. As mentioned in the introductory slides formulations using roller compacted granules show a decrease in tensile strength. Formulations with the Crospovidone grades, excipients typically used as disintegrant, show high tensile strengths. In fact they are comparable to formulations with Copovidones, which are usually applied as dry binders.

Higher levels of tensile strength are generally achieved when finer grades of Copovidone or Crospovidone are formulated. Cellulosic derivatives do not show such pronounced differences. In general however, the resulting tensile strengths are lower when compared to the PVP-derivatives.

Tablets formulated with Crospovidone disintegrate very quickly Figure 8a. A change in the disintegration time of tablets using the finest Crospovidone grades as dry binders is not visible. Thus roller-compact Crospovidone does not forfeit its capability to act as disintegrant.

Tablets manufactured using the granulated formulation of HPMC show a reduced disintegration time for the three selected compression forces, Figure 8b, which might be due to the lower tensile strength of the HPMC formulations.

Figure 9 illustrates another formulation, containing hydrochlorothiazide as API, lactose as filler (replacing the Ca-phosphate) and 9% of dry-binder. The compression into the tablets was performed at the same compression forces as in example 1. The tablets dimensions are as follows: Tablet weight 350mg and tablet diameter 12mm.

As for the placebo formulation it can be observed that finer grades of Crospovidone and Copovidone result in the highest tensile strengths too. For the coarse binders, the differences in tensile strength between powder and granulated starting material are less pronounced than for the fine binders. The selection of lactose monohydrate as filler and the presence of hydrochlorothiazide as API evened out the different level of tensile strength. Thus not only dry binders have a specific impact, but also the selection of filler in combination with the API to be formulated is a factor to be taken into account.

The next parameter to be looked at is the dissolution time. As obvious from Figure 10, the influence of roller compaction on dissolution is practically negligible with the exception of the HPC-based tablets. All other tablets made of roller compacted granules tend to have a slight delay regarding the onset of dis-

Figure 8a and 8b. Roller Compaction & Proper Excipient Selection: Case Study - Powder Blends vs. Dry granulated Mixtures - Impact on Disintegration Time [min]

- Disintegration time depends on compression force
- For Copovidone a prolongation of the disintegration time is seen only at 25kN compression force, for 18kN it is even reduced
- Disintegration time of HPMC based tablets using the granulated formulation was reduced.
- Negligible prolongation of disintegration time for micronized Crospovidone-type Kollidon CL-M when compacted granules are compressed to tablets.
- Disintegrant functionality of Crospovidones remains active in roller compacted granules.

Figure 9. Roller Compaction & Proper Excipient Selection: Case Study 2 – Formulation of HCT

HCT formulation 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide</td>
<td>7%</td>
</tr>
<tr>
<td>Binder</td>
<td>9%</td>
</tr>
<tr>
<td>Lactose</td>
<td>84%</td>
</tr>
</tbody>
</table>

solution, but the performance ranking of the individual binders stays unchanged, whilst the Crospovidones show the fastest dissolution behavior.

Based on the results, Kollidon VA 64 Fine, Kollidon CL-M as well as Kollidon CL-F as the most recommended dry binders for roller compaction. Products with the smallest particle sizes result in tablets with excellent tensile strengths. Crospovidone grades, usually applied as disintegrant, show a high efficiency as dry binder too.

Summary
Roller compaction is a widespread process in the pharmaceutical industry. It is suitable for the majority of APIs and offers a tremendous reduction of the production costs.

Selecting the proper binder is a key parameter in roller compaction formulation. Crospovidone offers bifunctional properties as dry binder and disintegrant. Product with high plasticity, such as Kollidon VA 64, allow the formulation of very hard tablets. In terms of binding capability and dissolution performance, the most recommended choices are Kollidon CL-M and Kollidon VA 64 Fine.

BASF offers comprehensive solutions to the pharmaceutical industry, ranging from a broad portfolio of excipients to active ingredients and custom synthesis services. With its expertise in polymer chemistry and research and development capabilities around the globe and the company’s clear commitment to developing pharmaceutical excipients, BASF continuously creates solutions that contribute to its customers' success. BASF’s high-quality ingredients and services can help with challenges related to Instant & Modified Release, Solubilization, Taste Masking, Soft Gels and Skin Delivery. BASF’s soft gel platform seeks to provide understanding, solutions and materials specifically targeted for soft gel application.