Colorcon®

WHITEPAPER

Streamline Manufacture of Modified Release Matrix Tablets via Direct Compression

Introduction to Matrix Tablets

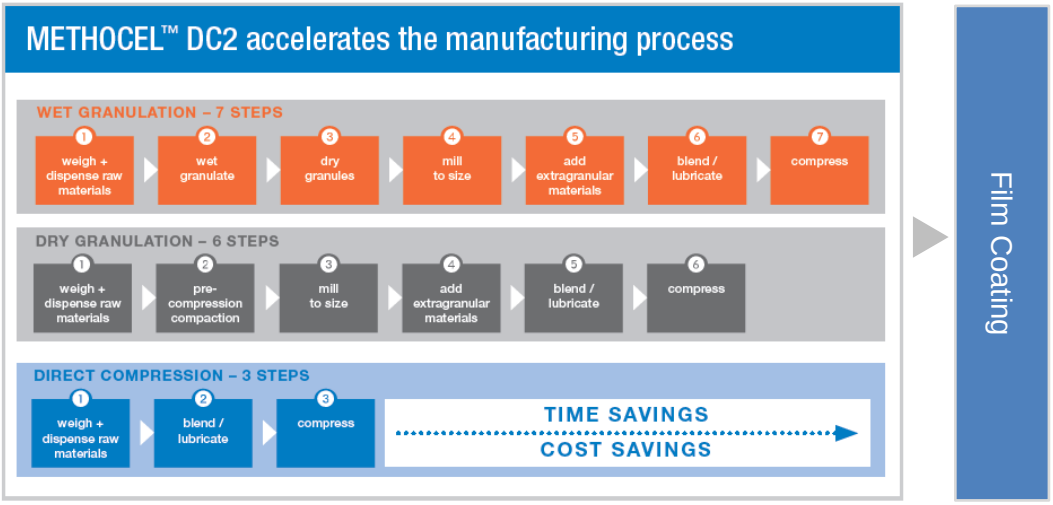
The hydrophilic matrix tablet is a well-known modified release oral solid dosage form that has been successfully utilized for several years. They can be employed to reduce dosing frequency as well as dampen the systemic C_{max} or plasma concentration, of an active pharmaceutical ingredient (API), which may prove beneficial if the API is prone to cause adverse effects at elevated systemic concentrations. Both aspects point to improved patient compliance and maximized therapeutic benefit.

For the drug product manufacturer, matrix tablets offer simplicity and elegance in terms of formulation development, ease and relatively low cost of manufacture when compared to more complex systems such as osmotic push-pull tablets.

Hypromellose (HPMC) is the most commonly employed polymeric excipient used to deliver modified release performance from a hydrophilic matrix tablet. HPMC is derived from cellulose pulp by substituting some of the hydroxyl groups in the anhydroglucose unit with methyl and hydroxypropyl ether substituents.

Matrix Tablet Manufacture

There are three main routes for manufacturing matrix tablets. Wet granulation is common but is a multi-step process that should not be used for API's that are moisture sensitive. Dry granulation is a slightly less complex process but is still laborious. Direct compression, by contrast, is a simpler three-step process and is the most streamlined of the tablet manufacturing processes, which essentially entails weighing and dispensing of raw materials, blending, and finally, tableting.



Direct compression with METHOCEL™ DC2 can deliver 60% savings in processing time and cost while providing better protection for heat- and moisture-sensitive actives.

Both dry granulation and direct compression require suitable powder blend flowability. If suitable flowability can be achieved, while minimizing powder blend segregation, direct compression is clearly the most simple, elegant, and streamlined of the manufacturing processes.

Balancing Performance Attributes

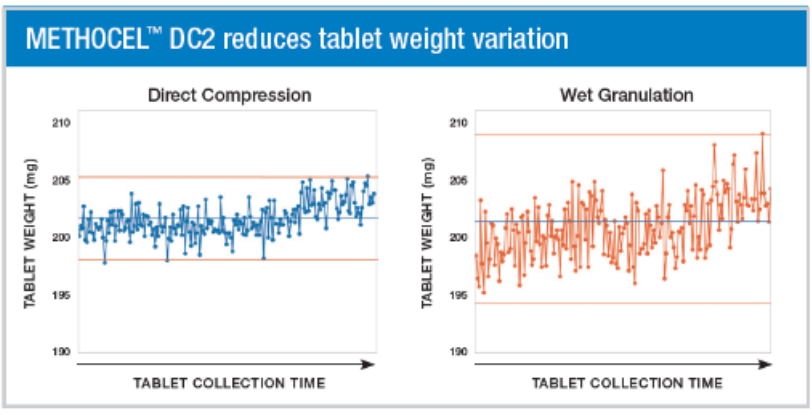
The following properties need to be considered when the hydrogel forming excipient is to be included in the formulation for a hydrophilic matrix tablet.

- **Maximum flowability**, which positively impacts formulation processability
- **Density** at a suitable range to maximize compatibility, while minimizing potential for segregation of formulation components
- **High permeability** to allow for maximum air displacement as the formulation is fed into the tablet press, through the powder feeder, and fed completely and fully into the die prior to tablet compaction
- **Small particle size** to facilitate formulation of a uniformly-distributed lattice of polymeric particles throughout the matrix tablet for uniform hydrogel formation upon exposure to gastrointestinal (GI) media
- **High hydrophilicity** to support rapid hydrogel formation upon exposure to GI media
- A **range of molecular weight grades** to allow the formulator to tune modified release performance from the matrix tablet, depending upon the properties of the API being formulated

These attributes must be balanced to achieve the most desirable balance of the performance properties.

Direct Compression with METHOCEL™ DC2

METHOCEL™ DC2 is produced using a proprietary manufacturing process to provide unique particle morphology. DC2 is pure, compendial HPMC and is the most flowable direct compression grade of HPMC available today. No other ingredients are added, and the flowability translates to streamlined production and improved process control during matrix tablet manufacture.



METHOCEL™ DC2 used in direct compression shows less variation in tablet weight over the tableting run than wet granulation processing.

There are many benefits of METHOCEL™ DC2 HPMC when used in both roller compaction and direct compression of tablets. Use cases range from high dose APIs, such as metformin hydrochloride tablets, through to tablets with superior unit dose content uniformity of a very low dose API such as indapamide.

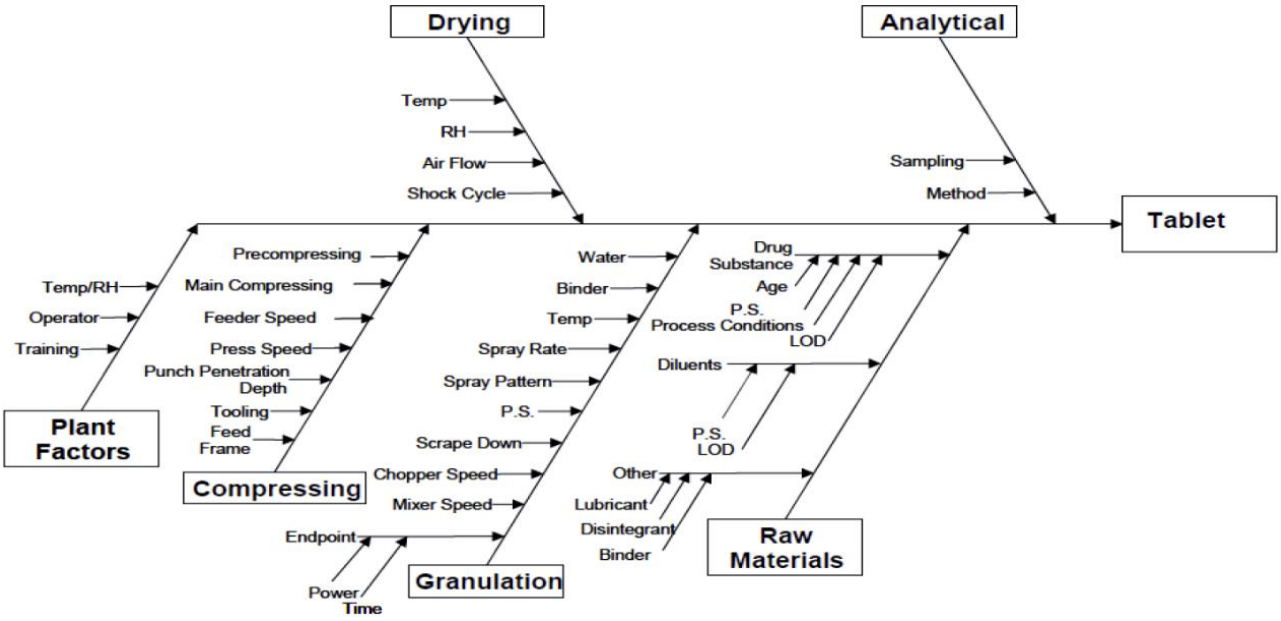
METHOCEL™ DC2 exhibits better flow in formulation blends compared to traditional HPMC-based formulations. Uniform die-fill during tablet manufacturing provides tighter tablet weight control and overall improved process capability.

The Case for Direct Compression over Granulation

Direct compression has the fewest steps and requires the least amount of equipment and time to manufacture, reducing the cost to manufacture. While total cost and profit are important drivers for using direct compression, there are other considerations. Hydrophilic matrix polymers pose a difficult challenge in manufacturing, especially when water is used during granulation.

Wet granulation is a multi-step process, requiring more equipment and space in your facility as well as additional operators to run and clean the machines, Figure 3. The biggest concern with granulation is the exposure of the formulation ingredients to heat as well as moisture. In some cases, this can cause degradation of the APIs or negatively impact the stability of the drug. Even with roller compaction, which is a dry granulation process, there can be heat exposure to the drug from the frictional and compaction forces to which the product is exposed.

Figure 1: Tablet Manufacture via Wet Granulation[1,2]



Common Problems with Wet Granulation

Liquid Addition

The right combination of spray rate and powder flux is needed to add the right amount of liquid to the granulator in a specific period. When wetted, these polymers will hydrate and form gels very quickly. These gels can be very viscous and can be difficult to break up or to disperse inside the granulator. By producing large agglomerates, there will be difficulty drying the granulation and potential problems in the milling step. Large agglomerates may not completely dry once the surfaces of the agglomerates become dry; this can then produce higher moisture in the final granulation after these particles are milled. Large particles tend to reside longer in the milling chamber and that produces a higher number of fines after the milling status is complete.

Use of Organic Solvents (Alcohol)

A common way to avoid large agglomerates is to avoid using water, which causes the rapid hydration of HPMC. Alcohol, alternatively used as a granulating fluid, will not swell the HPMC. While this can solve the agglomeration problems, many other issues arise from the use of organic solvents. The risk of explosion is serious when using large quantities of organic solvent. Specialized equipment and facilities are required for this and there may also be significant environmental controls placed on this type of operation depending on state, local, and federal regulations on emitting solvents. Solvents are often more expensive than water, so this will also increase the cost of the operation. Finally, the interaction with the solvent and the API and the residual solvent left in the product must also be understood as it can have significant impact on the product.

Process and Equipment

Granulation process parameters can also have a significant impact on granule properties, as well as tablet properties, once compressed. The most significant parameters would be the amount of water, the impeller speed, wet massing time, and the spray rate. These will influence the particle size in bulk density of the granulation.

Similarly, in roller compaction, parameters such as roll pressure, screw speed and role speed, can also impact particle size and granule density. When over densification of the granulation occurs, we will see a decrease in the compaction properties of that granulation resulting in lower tablet hardness.

Poor Formulation Practices

A common misconception is that HMPC as the controlled release polymer will bind granules together like a traditional low viscosity granulation binder. However, as these high viscosity polymers hydrate and swell when wetted with water the polymer surface becomes sticky and it picks up API particles and other excipients. When the polymer dries it typically shrinks back to its original size and many times the API breaks from the surface. This condition is exacerbated when larger particle size of APIs are used. With poorly balanced APIs in the granules, we may see segregation in the tablet press. Checking the assay of different sieve cuts on the granulation is recommended to understand the API uniformity in the granulation.

Breakthrough Technology – METHOCEL™ DC2 Premium Cellulose Ethers

This whitepaper outlines some of the complexities of wet granulation. Using high viscosity rate controlling polymers like HPMC add even more challenges to this process due to their inherent properties and high concentration in matrix formulation. This gives direct compression a positive outlook for manufacturing drug products by significantly reducing the complexity of the manufacturing process. When considering an ideal excipient, a balance of performance attributes is needed. METHOCEL™ DC2 is designed to offer this balance, providing improved dry powder flow and enabling shift to direct compression without a compromise of tablet quality.

METHOCEL™ DC2 premium excipients help you enjoy the benefits of powder processing techniques while maintaining consistent modified release performance.

References

1. ICH Q8, 2009, Pharmaceutical Development Q8(R2), http://www.ich.org
2. Nagar M, Singhai SK, Chopra VS, Bala I, Trivdei P (2010). Der Pharmacia Lettre 2(2), 370-392.

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