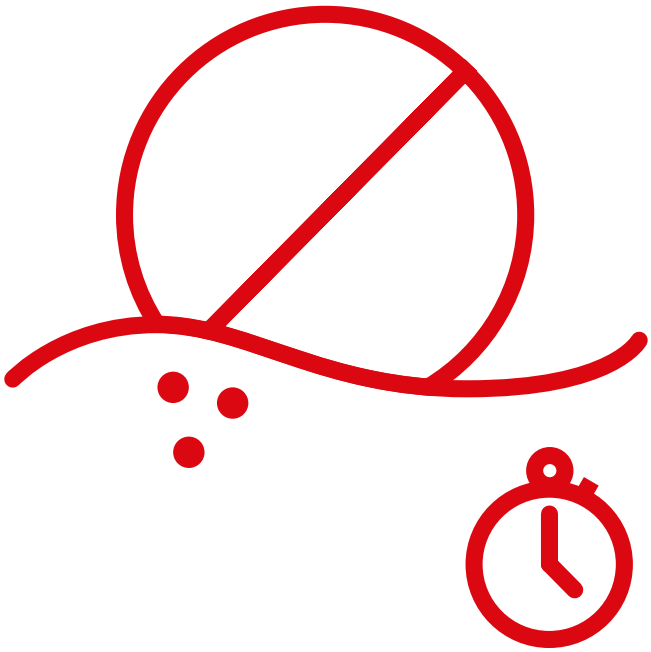
Pharma Solutions

White Paper

Dupont's Unique Polymer Portfolio and Deep Expertise Make Direct Compression of Controlled Release Tablets a More Efficient and Cost-Effective Reality



Extensive research shows that POLYOX™ and METHOCEL™ enable high-performing controlled release tablet formulations for direct compression, a discovery that puts customer convenience at the forefront.

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As the pharma industry trends toward a future of continuous manufacturing, drug developers are looking to save time, reduce the likelihood for human error and respond more nimbly to market changes. In addition, they're expected to meet ever-rising demand and stave off drug shortages.

Hydrophilic matrix tablets – which have long been the format of choice for optimal controlled release of APIs – are typically manufactured using a wet or dry granulation process, either of which can deliver the required powder flow properties needed for successful compression and robust formulations.

Direct compression could simplify production of hydrophilic matrix tablets, but this method historically has often been challenging due to poor flow properties and low compressibility of powder blends —until now. This whitepaper will reveal how DuPont Nutrition & Biosciences' unique portfolio and deep expertise can provide several options to make effective production of hydrophilic matrix tablets more convenient and cost-effective than ever.

Production methods at a glance

Granulation is a time-consuming technique that, while effective, can lead to product cross-contamination and product loss during processing. All of these factors make this method more costly than direct compression in terms of both time and expense.

Direct compression is the shortest, most effective and least complex way to produce tablets. A manufacturer can blend an API with excipients, followed by compression, which makes the product easy to process. No additional steps such as drying or sieving are required. But not all excipients hold up well during this process, which makes the selection of ingredients all the more critical.

Anatomy of a case study

The question remains: Can drug manufacturers simplify production of controlled release tablets through direct compression without compromising performance? The answer is a resounding "yes." Through extensive research, DuPont's experts have pioneered a way to harness polymer chemistry to effectively manufacture matrix tablets via a simple direct compression method.

Researchers conducted a case study using a particle-engineered grade of DuPont's proprietary form of hypromellose (METHOCEL™ Premium K100M, DC2) and a high molecular weight grade of its polyethylene oxide with inherently good flow properties (POLYOX™ WSR 301) for evaluation as rate-controlling polymers. Propranolol HCl was used as a soluble model drug.

Composition quick look

Matrix tablet formulations consisted of 20% w/w propranolol HCl as a model drug, 30% w/w hypromellose (METHOCEL™ Premium K100M, DC2) or polyethylene oxide (POLYOX™ WSR 301) as a release rate controlling polymer, 40% w/w microcrystalline cellulose (Avicel® PH102) and 9% Lactose monohydrate (Fast Flo®) as filler, 0.5% w/w colloidal silica (SiO_2, Cab-O-Sil®) as anti-adherent and 0.5% w/w sodium stearyl fumarate (Alubra® PG-100) as lubricant.

Into the lab

DuPont researchers began the study by using a laser diffraction particle size analyzer to measure the particle size distribution of the two rate controlling polymers, METHOCEL™ Premium K100M, DC2 and POLYOX™ WSR 301. Next, all ingredients were incorporated into 1-kg batches.

They pre-blended silicon dioxide with Avicel®, passing the subsequent mixture through a 20-mesh screen. The pre-blend silicon dioxide mixture, propranolol HCl and fillers were then passed through a conical mill at 2,500 rpm for de-lumping and to ensure uniform distribution of the drug. The final mix was blended with the rate-controlling polymer and lubricant in a 4-qt V-blender (with no intensifier bar) at 25 rpm for 15 minutes. They measured the bulk (pb, g/mL) and tap density (pt, g/mL) of each blend to obtain the Carr's Compressibility Index (Equation 1), in which lower values indicate better flow properties.

Equation 1.

$$\text{Compressibility Index} = 100\ \frac{p - b}{pt}$$

The team then compressed each blend into 400 mg tablets, and evaluated the tablets for physical properties, assay and content uniformity, hydration and gel properties, drug release and stability. They measured tablet properties, including weight and dimensions, manually. Once they had also measured crushing strength, friability and tensile strength, they set select tablets aside for further comparison studies.

They assessed the uniformity of dosage units by individually dissolving ten tablets into 100 g of methanol, followed by centrifugation and dilution of 2.5 g of supernatant with 50 g methanol. They then measured drug concentration at 290 nm in a 1 cm cell with a methanol blank.

Biorelevant dissolution testing was carried out using USP Apparatus 2 at 100 rpm with 0.1N HCl for 90 minutes, followed by media replacement with 900 mL pH 6.8 phosphate buffer.

Next, they measured polymeric hydration and gel strength from the prepared matrix tablets using a texture analyzer set to "Compression test mode." The instrument was equipped with a flat-end, cylindrical acrylic probe with a half-inch diameter to measure force while traveling downward onto the hydrogel formed by polymer hydration. To prepare samples for texture analysis, they manufactured placebo tablets of METHOCEL™ Premium K100M, DC2 and POLYOX™ WSR 301 using a compaction simulator. Active tablets with the same TS were also tested for gel strength. The tablet samples were hydrated in 0.1N HCl (2h) and transferred into DI water (25 ml) followed by testing at 1, 3, 5 and 24 hours after DI water hydration. All samples were tested in triplicate at each time interval.

Promising results

Researchers found clear differences in particle size distribution, densities and flow properties of the formulation blends. The METHOCEL™ powder with smaller mean particle size (85 µ) contributed to the higher tapped density of the blend and the higher Carr index (18). As expected, POLYOX™ with a larger mean particle size (177 µ) contributed to the lower Carr index (7.3), lower tapped density and improved flow properties of the POLYOX™ formulation blend.

Regardless of the differences in blend flow properties, both tablet formulations demonstrated low weight variation with an RSD of less than 0.5%, which indicates satisfactory flow properties of the blends.

Uniformity of dosage-unit testing for the METHOCEL™ Premium K100M DC2 matrix tablet samples displayed a mean weight of propranolol HCl of 80.8 ± 1.5 mg/tablet (n=10) or 101.0 ± 1.9% of the 80 mg label claim. The calculated USP acceptance value (AV) of 4.5 satisfied the USP requirement of less than or equal to the maximum allowed acceptance value (L1) of 15.0. For the POLYOX™ WSR 301 matrix tablets, the mean weight of propranolol HCl was 81.6 ± 0.8 mg/tablet (n=10) or 102.0 ± 1.1% of the 80 mg label claim. The calculated AV of 2.5 satisfied the USP requirement of less than or equal to the maximum allowed acceptance value (L1) of 15.0.

Researchers found the extended drug-release profiles of both tablet formulations to be robust. While the propranolol HCl release from POLYOX™-based tablets was slightly faster, the difference wasn't significant and both profiles were similar with an f2 similarity factor—a measure of the closeness between two dissolution profiles—greater than 71.

Looking at the stability study of both tablet formulations, researchers indicated no significant changes in drug release after one month of storage under accelerated conditions (40 °C/75% RH).

Upon studying hydration, researchers found that POLYOX™ hydrates faster and becomes softer than METHOCEL™ Premium K100M, DC2. This observation was also reflected in gel strength studies, as less force is needed for the probe to travel into the POLYOX™ gel layer when compared to the METHOCEL™ gel layer surrounding the tablets.

What does it all mean?

Both METHOCEL™ and POLYOX™ resulted in good flow properties in their respective blends, with each polymer displaying unique properties that offer formulators different possibilities.

For example, POLYOX™ tablet formulations demonstrated higher tablet hardness and tensile strength, which indicates higher compactability; METHOCEL™, on the other hand, enabled greater gel strength, which is preferable when formulating with a highly soluble API.

Manufacturers hoping to use both in combination can reference the patent, "Optimal polymer mixtures for gastric retentive tablets," which demonstrates how, by combining polyethylene oxide and hydroxypropyl methylcellulose as a matrix, researchers developed an excellent swellable, sustained-release tablet with several unique benefits. Researchers found that, when combined, the polymers could exist in lower amounts in the tablets, compared with solo use of either polymer. In addition, these tablets retained the swelling behavior of polyethylene oxide, balanced against the erosion behavior of hydroxypropyl methylcellulose. This modulated the extent and progress of tablet swelling, offering improved control and reliability, while retaining the tablet's ability to swell for gastric retention and to control drug release.

It all comes down to indispensable ingredients and technical expertise

As the case study shows, DuPont's formulations demonstrate high tablet tensile strength, low tablet friability, good content uniformity and great blend flow properties. The propranolol HCl release profile from both matrix tablets are similar and remain stable after one month of storage under accelerated stability conditions.

While METHOCEL™ and POLYOX™ differ slightly in their respective benefits, manufacturers have the flexibility of using one or both polymers to facilitate matrix tablet manufacturing via a direct compression process. By using an efficient and cost-effective process, and aided by DuPont's deep polymer and technical expertise, manufacturers can ensure their formulations deliver better performance.

This discovery is yet another demonstration of how DuPont's expertise can help customers excel, presenting manufacturers with a clear path toward greater savings of both time and money.

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