POLYMER CHEMISTRY'S INFLUENCE ON CONTROLLED-RELEASE TABLETS MANUFACTURED VIA DIRECT COMPRESSION

In this case study, Nasrin Mahmoudi, PhD, PharmD, Technical Service Manager, Pharmaceutical Application and Innovation; Kevin McIntyre, Pharmaceutical Applications Supervisor; Joseph Lee, Research Associate; Holly Bertrand, Research Chemist; Yeli Zhang, PhD, Technical Service Manager; Fernanda Onofre, PhD, Americas Regional Applications Leader; and Amina Faham, PhD, Global Director, Applications Development and Innovation, all at DuPont Nutrition and Biosciences, investigate the effect of a simple direct compression method on controlled-release matrix tablet formulations.

It is common industry practice to produce hydrophilic matrix tablets using a wet or dry granulation process. Either method will help achieve the required powder flow properties for a successful compression and a robust formulation, but compared with those relatively complicated processes, simple direct compression manufacturing is preferred. In a controlled-release matrix tablet formulation, hydroxypropyl methylcellulose (hypromellose) and polyethylene oxide are often used as key polymer excipients to control drug release. The chemical, physical and mechanical properties of these polymers have significant influence on manufacturing processes and product attributes.

In the case study that follows, we will examine discoveries made by the research team at DuPont Nutrition and Biosciences (DuPont) on the influence of polymer chemistry in matrix tablet performance manufactured through a simple direct compression method. A particle-engineered grade of DuPont's proprietary form of hypromellose (METHOCEL™ K100M DC2) and a high-molecular-weight grade of its polyethylene oxide with inherently good flow properties (POLYOX™ WSR-301) were selected for the evaluation as rate-controlling polymers. Propranolol hydrochloride was used as a soluble model drug.

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A Look at Composition

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®) as lubricant.

Preparing the Powder Blend

The research team began by incorporating the ingredients into 1 kg batches. They preblended silicon dioxide with Avicel®, passing the subsequent mixture through

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a 20-mesh screen. The preblend silicon dioxide mixture, propranolol HCl and fillers were then passed through a conical mill (Quadro® Comil® Scalable Lab System) 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.

Powder Blend Testing

Particle size distribution of the rate-controlling polymers – METHOCEL™ Premium K100M DC2 and POLYOX™ WSR-301 – were measured using a laser diffraction technique.

The bulk and tapped densities of each blend were measured to obtain Carr's Compressibility Index (Equation 1), an indication of the flowability of a powder in which lower values indicate better flow properties; and the Hausner ratio (Equation 2), a number correlated to the flowability of granular material where Vt is the tapped density of powder (g) and Vb is the bulk density (mL).

Equation 1

$$Compressibility\ Index = 100 \times \left(\frac{Vt-Vb}{Vt}\right)$$

Equation 2

$$Hausner\ Ratio = \frac{Vt}{Vb}$$

Time for Compression

Each blend was compressed into 400 mg tablets on a four-station Korsch rotary tablet press, using a 13/32 SRC tooling at a turret speed of 20 rpm. A compression profile was generated at five compression forces (4, 6, 8, 10 and 12 kN). The resulting matrix tablets were evaluated for physical properties, assay and content uniformity, hydration and gel properties, drug release and stability. Tablet properties, including weight and dimensions (n=5), were measured manually. Crushing strength was measured using a Dr Schleuniger 8M Pharmatron tablet hardness tester. Friability of tablets (n=16) was performed at 100 drops using a VanKel 45-2000 friability tester, according to USP. Tensile strength (TS) of tablets was calculated, and tablets with TS of 2 MPa were selected for further comparison studies.

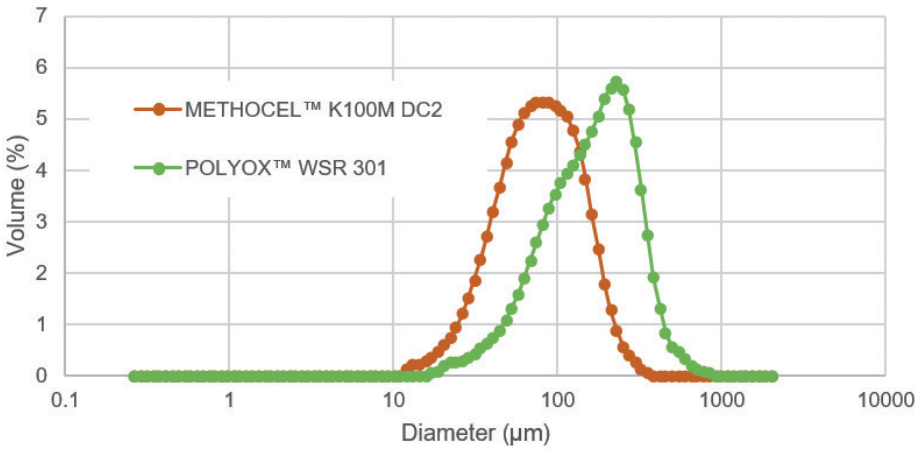

Figure 1: Particle size distribution of METHOCEL™ Premium K100M DC2 and POLYOX™ WSR-301.

ID	Description	Bulk Density g/cc	Tapped Density g/cc	Carr's Compressibility Index (%)	Hausner ratio
F1	Propranolol/METHOCEL™ K100M DC2	0.44	0.54	17.8	1.2
F2	Propranolol/POLYOX™ WSR-301	0.46	0.50	7.3	1.1

Table 1: Formulation blends properties.

The uniformity of each tablet was assessed by dissolving them one by one (n=10) into 100 g of methanol, followed by centrifugation and dilution of 2.5 g of supernatant with 50 g methanol. Drug concentration was measured by UV spectroscopy 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 a buffer of 0.1N HCl for 90 minutes, followed by media replacement with 900 mL pH 6.8 phosphate buffer.

Hydration Properties and Gel Strength

The DuPont team measured polymeric hydration and gel strength from the prepared matrix tablets using a Stable Micro System TA-XT2 Plus texture analyser set to "compression test mode". The instrument was equipped with a flat-end, cylindrical acrylic probe with a half-inch (1.27 cm) diameter to measure force while travelling downwards onto the hydrogel formed by polymer hydration. To prepare samples for texture analysis, placebo tablets of METHOCEL™ K100M DC2 and POLYOX™ WSR-301 were manufactured using a compaction simulator targeting a TS of 2 MPa. The 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 deionised (DI) water (25 mL) followed by testing at one, three, five and 24 hours after DI water hydration. All samples were tested in triplicate at each time interval.

Results

Figure 1 shows particle size distribution of the release-rate-controlling polymers, METHOCEL™ Premium K100M DC2 and POLYOX™ WSR-301. Densities and flow indices of both formulation blends are shown in Table 1. Clear differences in particle size distribution, densities and flow properties were found. The METHOCEL™ powder with smaller mean particle size (85 µm) contributed to the higher density of the blend and the higher Carr index (18). As expected, the POLYOX™ with a larger mean particle size (177 µm) 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.

Tabletability of the propranolol tablet

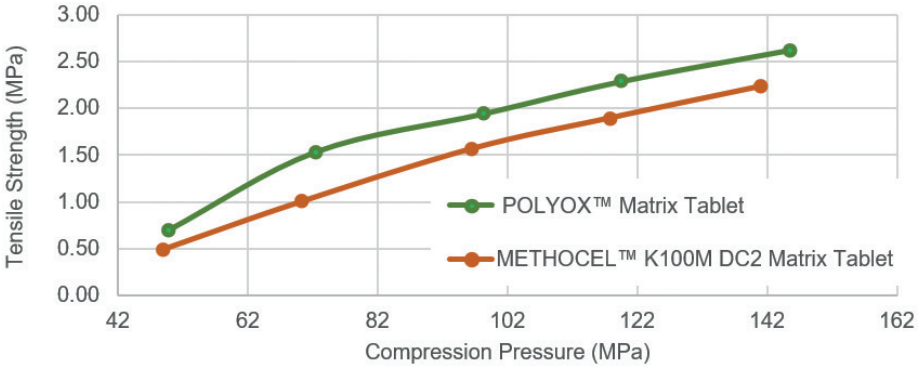

Figure 2: Tabletability of the propranolol formulation.

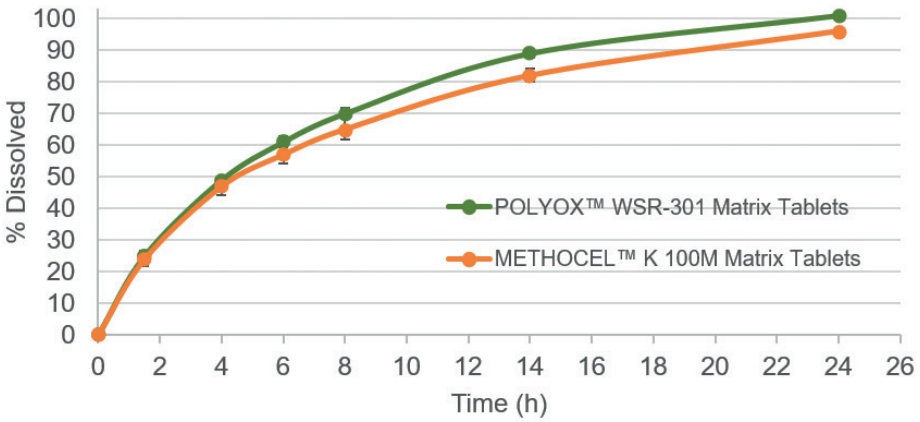

Figure 3: Comparative dissolution profiles of propranolol tablets.

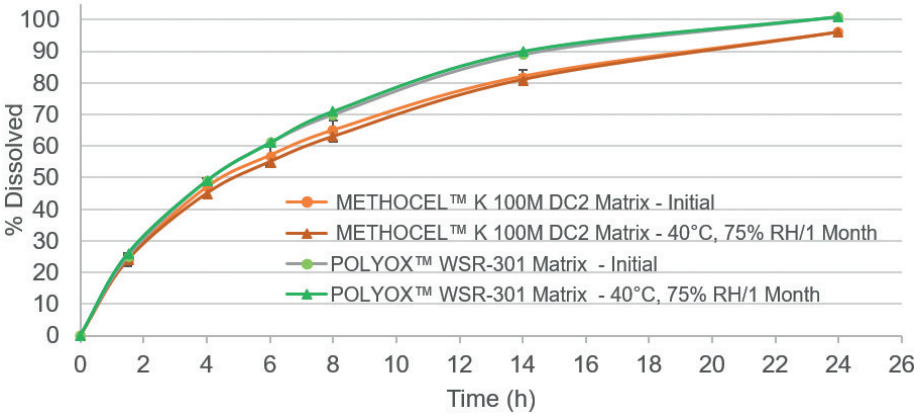

Figure 4. Comparative dissolution profiles of propranolol tablets - stability evaluation.

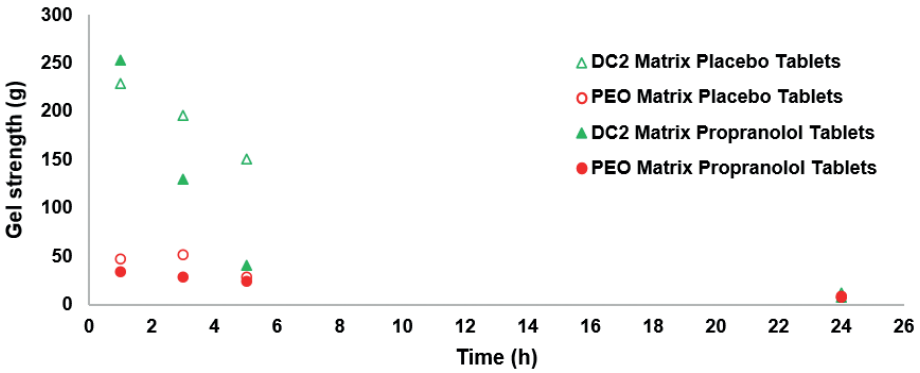

Figure 5. Comparative gel strength of METHOCEL™ K100M DC2 tablets and POLYOX™ WSR-301 tablets.

formulations are shown in Figure 2. POLYOX™ tablet formulations demonstrated higher tablet hardness and tensile strength, which indicates higher compactability of the POLYOX™ polymer with no influence on performance demonstrated by comparable dissolution (Figure 3).

Friability of both tablets was low, 0.1% (TS, 2.24 MPa) and 0.06% (TS, 2.63 MPa) for the METHOCEL™ and the POLYOX™ formulations, respectively.

Uniformity of dosage-unit testing for the METHOCEL™ 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 USP AV of 2.5 satisfied the USP requirement of less than or equal to the maximum allowed acceptance value (L1) of 15.0.

The extended drug-release profiles of both tablet formulations were shown to be robust, as shown in Figure 3. While the propranolol HCl release from POLYOX™-based tablets was slightly faster, the difference was not significant and both profiles were similar with an f2 similarity factor – a measure of the closeness between two dissolution profiles – greater than 71.

The stability study of both tablet formulations indicated no significant changes in drug release after storage for one month under conditions of accelerated stability. The comparative dissolution profiles of the tablets are shown in Figure 4.

Studying hydration showed that POLYOX™ hydrates faster and becomes softer than METHOCEL™ K100M DC2, an observation found in gel strength studies as well. As shown in Figure 5, less force is needed for the probe to travel into the POLYOX™ gel layer as compared with the METHOCEL™ gel layer surrounding the tablets.

Direct Compression Success

DuPont successfully employed METHOCEL™ K100M DC2 and POLYOX™ WSR-301 to manufacture matrix tablets using a simple direct compression method. The two robust matrix tablet formulations for propranolol HCl,

> "Both formulations demonstrated high tablet tensile strength, low tablet friability, good content uniformity and great blend flow properties."

a soluble model drug, were studied in parallel. Both formulations demonstrated high tablet tensile strength, low tablet friability, good content uniformity and great blend flow properties. The propranolol HCl release profiles from both matrix tablets were similar and remained stable after one month of storage under accelerated stability conditions. The investigation demonstrated that both polymers may be successfully used in matrix tablet manufacturing via a direct compression process, which is more cost-effective than dry or wet granulation methods. This has lasting implications for an industry in which simplicity can greatly increase the speed to market of potentially life-saving drugs.

ABOUT THE COMPANY

DuPont (NYSE: DD) is a global company with technology-based materials, ingredients and solutions that help transform industries and everyday life. DuPont's employees apply diverse science and expertise to help customers advance their best ideas and deliver essential innovations in key markets including electronics, transportation, construction, water, health and wellness, food and worker safety.

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Nasrin Mahmoudi, PhD, PharmD, is a member of the Application Development and Innovation (AD&I) scientists' team at DuPont Nutrition & Biosciences. She manages customer technical service requests in North America, develops applications for DuPont excipients, contributes to innovation projects and presents related information to customers, enabling them to troubleshoot and facilitate their formulations development process. Dr Mahmoudi earned her PharmD and PhD degrees from Tehran University of Medical Sciences (Iran) and completed post-doctoral research at Rutgers University (NJ, US) and Pfizer (NY, US). She has more than 17 years of experience in the pharmaceutical industry, particularly in solubility enhancement, and immediate- and controlled-release dosage forms.

Kevin McIntyre is Pharmaceutical Applications Research Laboratory Supervisor at DuPont Nutrition and Biosciences. His career spans 20+ years in the industry, including over 10 years in R&D / Process Engineering at Teva Pharmaceuticals (Israel). His expertise is used to optimise trial design and execution within the laboratory, and ensures DuPont standards are being met.

Joseph T Lee Jr is a Research Associate in the Pharmaceutical Solutions division of DuPont Nutrition & Biosciences. He is a graduate of the University of Scranton (PA, US) with a career spanning 40 years in the industry. Formerly, Mr Lee provided three decades of vital analytical support in the Health and Nutrition division of FMC Corporation (PA, US). He held previous positions in the Metals department at NMS Labs (PA, US), the Dissolution laboratory at Wyeth Pharmaceuticals (PA, US) and the Analytical department at Microbiological Associates (MD, US) providing testing for the National Institutes of Health. Analytical techniques include dissolution testing, spectroscopy, microscopy and chromatography.

Holly P Bertrand is a Principal Scientist at DuPont Nutrition and Biosciences. She is a graduate of Rutgers University (NJ, US) with over 25 years of analytical experience in rheology (suspension and powder), thermal (DSC, TMA, TGA), texture analysis, particle size analysis, Brunauer-Emmett-Teller (BET) surface area and microscopy. In her current role, she provides analytical support for both food and pharmaceutical project teams in new product development, as well as critical support work for manufacturing, sales and marketing.

Yeli Zhang, PhD, is a technical service manager in the pharma solutions division of DuPont Nutrition and Biosciences. Prior to her current role, Dr Zhang worked at FMC in the health and nutrition business, where she began as a senior scientist in excipient product development and support. She would later become North America Health Technical Manager, responsible for providing technical support on FMC's excipients to North American pharmaceutical companies. Before joining FMC, Dr Zhang worked at National Starch and Chemical Company (now Ingredion) (IL, US) as a senior scientist in areas of starch excipient and delivery system development.

Fernanda Onofre, PhD, is Americas Regional Applications Leader at DuPont Nutrition and Bioscience. Dr Onofre joined FMC in 2010, transferring to DuPont in 2017, taking on the role of Americas Regional Applications Leader for Pharma Solutions, heading the Technical Teams and Applications Labs in both North and Latin America. During her career, Dr Onofre led the customer Technical Support and all Technical-related activities in the EMEA and LATAM regions. She holds a PhD and a MSc in Food Science from the University of Arkansas (US), where she worked with food ingredients in pharmaceutical applications. She is a licensed pharmacist, graduated from the Universidade Federal do Ceará (Brazil).

Amina Faham, PhD, is DuPont's Global Director of Pharma Application Development and Innovation. She also chairs the DuPont Diversity and Inclusion Steering Committee. She earned her PhD in Pharmaceutics from Aix-Marseille University (France), People Leadership certification from INSEAD (Fontainebleau, France) and Leadership through financial excellence certification from MIT Sloan School of Management (Cambridge, MA, US).