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Investigation and rank-ordering of hydroxypropyl methylcellulose (HPMC) properties impacting controlled release performance

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A B S T R A C T

Hydroxypropyl methylcellulose (HPMC) is a commonly used excipient to enable controlled release (CR) performance from a hydrophilic matrix tablet. Quality-by-Design (QbD) initiatives have prompted formulators to proactively characterize and account for variabilities in process parameters and ingredient properties that could impact dosage form performance. Some excipient properties are referred to as functionality-related characteristics (FRCs), which could impact manufacturing or performance of the dosage form. HPMC FRCs include.

- Particle morphology (e.g. particle size)
- Methyl substitution (%Me)
- Powder flowability
- Hydroxypropyl substitution (%HP)
- Molecular weight (characterized as viscosity)

This study investigated the batch-to-batch variability of twenty HPMC 2208 (METHOCEL^{TM} K4M) batches produced across a time period of three years and the effect of FRC variability on CR performance. The study also examined the potential of using rheological characterization as a proxy for CR performance. The key findings were:

- FRC variability was very low from batch to batch, and CR performance was reproducible.
- %HP substitution was found to be the most significant FRC impacting CR performance, followed by 2 % viscosity.
- Particle size and %Me substitution did not significantly impact matrix tablet performance within the ranges investigated.
- Paracetamol release increased with increasing %HP content, but over a relatively narrow release range.
- From the studied rheological attributes the powder dissolution temperature (PDT) was found to be a promising proxy for CR performance. Further investigation is needed to determine the strength of the correlation

1. Introduction

Functionality-related characteristics (FRCs) are recognizable attributes that act as performance-indicating parameters for an ingredient used as an excipient [1]. In other words, FRCs are critical-to-quality attributes (CTQs) of the excipient, which could affect manufacturability and performance of the formulation [2].

HPMC is commonly used as a functional excipient to enable controlled release (CR) performance from a hydrophilic matrix tablet. HPMC FRCs include [1].

- Particle morphology (e.g. particle size)
- Powder flowability
- Molecular weight (typically characterized as viscosity of a 2 % aqueous solution at 20 °C)
- % Me substitution
- % HP substitution

QbD initiatives have prompted formulators to proactively characterize and account for variabilities in active pharmaceutical ingredient (API), excipient, and manufacturing process that impact dosage form production, quality, and/or performance [3–5]. This study investigates

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impacts of variability in HPMC FRCs. Study objectives were to.

- Investigate batch-to-batch variability of twenty commercial HPMC 2208 (METHOCEL^{TM} K4M) batches produced over a time period of three years and the effect of FRC variability on CR performance from a hydrophilic matrix tablet formulation.
- Rank-order HPMC FRCs impacting CR performance.
- Investigate rheology as a proxy to predict CR performance.

1.1. Background

Formulators have documented several approaches for investigating the impacts of HPMC FRCs on matrix tablet performance.

1.1.1. Particle morphology

Several researchers investigated how morphological differences in HPMC impact matrix tablet performance [6–8]. For example, aspirin was formulated into a monolithic matrix tablet containing the 50 mPa s viscosity grade of HPMC 2910 [6]. Two different morphologies were investigated.

- Fine, ball-milled HPMC: 95 % of the powder passed through a 100-mesh sieve.
- Coarse HPMC (not ball-milled): 84 % of the powder failed to pass through a 100-mesh sieve.

Aspirin release was complete within 1 h from matrix tablets formulated with coarse HPMC, whereas controlled release over 9 h was attained from matrix tablets formulated with fine HPMC.

1.1.2. Molecular weight/viscosity

Several groups have investigated the impact of HPMC molecular weight / viscosity on matrix tablet performance [9–14]. In a study published by Khanvilkar et al. [10], batches of 15,000 mPa·s viscosity grade HPMC 2208 were compared to various mixtures of 100 mPa s and 100,000 mPa·s viscosity grades of HPMC 2208. Matrix tablets formulated with the mixtures exhibited comparable CR performance to matrix tablets formulated with the 15,000 mPa·s viscosity grade. Khanvilkar et al. concluded that lot-to-lot variability in HPMC apparent viscosity exhibited minimal impact on CR performance.

1.1.3. Substitution

Documented in the literature are two primary approaches of investigating the impact of HPMC substitution on CR performance from matrix tablets. Some groups have investigated the impact of HPMC substitution from chemistry-to-chemistry [15–23]. Other groups have investigated the impact of substitution within a particular chemistry, such as HPMC 2208, which is the most common HPMC chemistry used to formulate matrix tablets [24–30]. Examples from both approaches are outlined below.

Velasco et al. investigated matrices containing propranolol HCl and varying concentrations of 4000 mPa·s viscosity grades of HPMC 2208, 2910, 2906, and methylcellulose in 0.1 N HCl, pH 7.4 phosphate buffer and water [19]. In general, controlled release was best achieved using the 2208 and 2906 chemistries. Matrices containing HPMC 2910 or methylcellulose failed to modify API release in at least one of the dissolution media tested.

Rajabi-Siahboomi et al. studied water mobility in the hydrated layer of a monolithic matrix that had been formulated using 4000 mPa·s viscosity grades of HPMC 2208, 2906, and 2910 [18]. Nuclear magnetic resonance (NMR) imaging was used to quantitate the water mobility gradient across the hydrated layer, which was similar in thickness regardless of HPMC chemistry. Towards the outer edges of the hydrated layer, the self-diffusion coefficient and T2 relaxation time approached that of free water, but the values decreased progressively moving in towards the hydration front. Significantly lower values were observed when HPMC 2208 was used. Referencing a previous study by Alderman [31], where HPMC 2208 provided the slowest API release, Rajabi-Siahboomi et al. proposed that the mechanism for more efficacious controlled release might be due to the fact that HPMC 2208 offered a greater diffusional resistance to water within the inner region of the hydrated layer than the other chemistries.

Viridén, Larsson, Wittgren, and co-workers published several studies regarding the impact of substituent heterogeneity on monolithic matrix hydration, erosion, and CR performance [25–30]. Most of their studies were focused on seven batches of 100 mPa·s viscosity grade HPMC 2208, sourced from two HPMC manufacturers. One batch exhibited significantly lower HP substitution than the other batches. In general, Viridén and co-workers observed that matrix hydration and subsequent erosion decreased with increasing substituent heterogeneity. The HPMC batch exhibiting lower HP substitution was also found to be more heterogeneously substituted, so substituent heterogeneity apparently was inversely proportional to extent of HP substitution.

Dong and Jian investigated the impacts of substitution, particle size, and viscosity grade of HPMC 2208 on release of three model APIs from monolithic matrices [24]. They observed some effects of particle size and viscosity but a more marked effect from HP substitution. For captopril and chlorpheniramine maleate, rate of API release decreased with increasing HP content. For indomethacin, rate of API release increased with increasing HP content.

Dahl et al. investigated the impact of varying physicochemical properties of HPMC on matrix performance [32]. Investigation of seven batches from two suppliers of 15,000 mPa·s viscosity grade HPMC 2208 revealed that HP content, in particular, exhibited a marked impact on CR performance. HP content and naproxen release rate ranged from 5.3 to 11.1 % and 0.12 to 0.27 $h^{-0.5}$, respectively. A direct correlation was observed between HP content and naproxen release.

Watt and Newhard formulated an optimized monolithic matrix containing tetracycline and 50 mPa·s viscosity grade HPMC 2910. They focused on HP substitution to optimize CR performance, and found that API release rate increased with increasing HP content [33]. They identified 8.3–9.8 % as the HP content range necessary to achieve optimal CR performance.

Judging from the breadth of the research described above, formulators have strived to better understand how HPMC FRCs impact matrix tablet performance. They recognized the extent to which batch-to-batch variations in FRCs could impact CR performance, and they subsequently designed dosage forms exhibiting sufficient robustness to accommodate those variations.

2. Experimental

2.1. Materials

Paracetamol was obtained from Spectrum Chemical Mfg. Corp., USA, and lactose (Flow-Lac 100) was obtained from Meggle Pharma GmbH (Leonburg, Germany). Talc and magnesium stearate were obtained from AppliChem GmbH (Darmstadt, Germany). All HPMC materials used were commercial HPMC 2208 (METHOCEL™ K4M), and all batches met METHOCEL™ CR grade specifications (2010 METHOCEL™ Product Information). All reagents used were of the highest purity available and purchased from Fluka (Seelze, Germany), Sigma-Aldrich (Seelze, Germany), or Merck (Darmstadt, Germany).

2.2. Statistical software

Statistical software used was JMP 18 from SAS (Cary, NC, USA).

2.3. Standard characterization of HPMC

%Me and %HP substitution were determined using Zeisel

methodology [34]. Viscosity was determined according to USP 43-NF 38 [35]. Salt was determined according to ASTM D2363-79 [36]. Particle properties were characterized using a RapidVue image analyzer (Beckman Coulter, Brea, CA, USA).

2.4. Preparation and characterization of granulations and tablets

2.4.1. Wet granulation

Paracetamol, HPMC, and lactose were wet-granulated with 23 % water using a 6-L high-shear granulator (main blade 300 rpm, side blade 600 rpm, Diosna Pharma Mixer, Diosna GmbH, Osnabrück, Germany). The granular materials were sieved through a 2-mm mesh screen, dried at 40 °C until residual moisture was ≤4 % and co-milled at 250 rpm through a 1-mm screen (Bohle Turbo Sieve BTS 100, L. B. Maschinen + Verfahren GmbH, Ennigerloh, Germany). Granule size characteristics were determined by laser diffraction (Sympatec HELOS/KR, Sympatec GmbH, Clausthal-Zellerfeld, Germany). Talc was added to the granular materials for the determination of flow properties. Compressibility index was measured with a powder tester (Micron powder tester PT-S, Hosokawa Alpine AG, Augsburg, Germany).

2.4.2. Tablet compaction

Samples from twenty HPMC 2208 commercial batches were formulated and compacted to matrix tablets containing 50 % paracetamol, 30 % HPMC, 18 % lactose, 1 % talc, and 1 % magnesium stearate. Paracetamol, HPMC, and lactose were wet-granulated as described in previous section. Talc and magnesium stearate were added subsequently and blended for 10 min and 1 min, respectively. Tablets (13/32 inch FFBE, 10.8-mm diameter by 3.9-mm thickness) were compressed using a Kilian rotary press (Kilian Pressima 8, IMA Kilian Gmbh & Co. KG, Köln, Germany). Weight and hardness targets were 500 mg and 90 N, respectively. Tablet hardness was characterized using an Erweka TBH 325-WTD (Erweka GmbH, Heusenstamm, Germany).

2.4.3. CR performance testing

Dissolution testing buffer was prepared, as necessary, by weighing 34.03 g KH_2PO_4 and 0.72 g NaOH in a flask, filling up to 5 L with deionized (DI) water, and sufficiently agitating to ensure salt dissolution and solution uniformity. Each tablet was first secured in a sinker and then dissolution testing (n = 6 for each tablet batch) was conducted in 900 mL of pH 5.7 phosphate buffer for 22 h at 37 °C using an Erweka Dissolution Tester 626, (Erweka GmbH) equipped with standard USP 2 paddles rotating at 50 rpm. The absorbance of paracetamol at each sample time point was measured using a Shimadzu UV–Vis spectrophotometer (Shimadzu Deutschland GmbH, Duisburg, Germany). The concentration of paracetamol was calculated using a standard calibration curve at a wavelength of 243 nm.

2.5. Rheological characterization

2.5.1. Powder dissolution temperature (PDT)

The PDT measurements were performed with a UDS 200 rheometer (Anton Paar, Ostfildern, Germany). Cup (Couette) Z-3 geometry with a wing stirrer was used. Amounts of water and HPMC were used to achieve a concentration of 1.5 % w/w. Water (29.55 g) was added into the cup and heated to 80 °C. Once 80 °C was attained, the sample (0.45 g) was slowly added. HPMC is insoluble at this temperature. The suspension was stirred at 500 rpm for 60 s. After a uniform suspension was achieved, the temperature was decreased at a cooling rate of 1 °C/min while stirring at 300 rpm. The torque was recorded at four data points/min. At a characteristic temperature the torque starts to increase, which represents the onset of the PDT. The measurements were continued until a temperature of 10 °C was reached.

2.5.2. Shear viscosity and gelation temperature

Solution Preparation. A 2 % (w/w) aqueous solution of HPMC was produced by dispersing the dry powder at room temperature in the appropriate amount of water while stirring at about 1500 rpm for at least 1 h. The solution was stored overnight at 5 °C.

Shear Viscosity. Shear viscosity experiments were performed at 20 °C using an MCR 501 rheometer (Anton Paar, Ostfildern, Germany) with Peltier system and cone-and-plate geometry (CP50-1/TG) with a gap of 0.049 mm. Viscosity was analyzed in a flow curve experiment over a shear rate range of 1–1000 s^{-1} with five measurement points per decade (logarithmic scale).

Precipitation and Gelation Temperatures. A temperature sweep experiment measured solution precipitation and gelation temperatures using an MCR 501 rheometer (Anton Paar, Ostfildern, Germany) with a cup-and-bob geometry (CC-27) in oscillation shear flow. The measurements were performed at constant frequency, v, of 2 Hz and constant strain (deformation), γ, of 0.5 % in the linear viscoelastic region from 20 to 90 °C with a heating rate of 1 °C/min and a data collection rate of four points/min.

The storage modulus, G′, which is obtained from the oscillation measurements, represents the elastic properties of the solution. The loss modulus G″ represents the flow properties of the solution. The precipitation temperature is analyzed from a plot of log G′ vs. temperature as the crossover of two tangents. The first tangent is fitted to the decrease of the storage modulus with increasing temperature, and the second tangent is fitted to the sharp drop in storage modulus above 65 °C. The onset gelation temperature (G'_{min}) of HPMC is taken from the minimum of the storage modulus. After gelation onset and during the gelation process, G′ increases at higher temperatures and therefore the crossover (G′ = G″) of both moduli is detected.

2.6. Chemical structure analysis of HPMC

Chemical structure analysis was conducted via a perethylation process. HPMC (10–12 mg) was dissolved in 4.0 mL of dry analytical-grade dimethylsulfoxide (DMSO) (supplied by Merck and stored over 0.3-nm molecular sieve beads) at about 90 °C with stirring and then cooled to room temperature. The solution was stirred at room temperature overnight to ensure complete dissolution. HPMC dissolution was performed under a dry nitrogen atmosphere in a 4-mL vial with screw cap. The dissolved HPMC was transferred to a 22-mL vial with screw cap to begin the perethylation process under a dry nitrogen atmosphere. Powdered sodium hydroxide (freshly ground with mortar and pestle, analytical grade, Merck) and ethyl iodide (synthesis grade, stabilized with silver, Merck-Schuchardt, Hohenbrunn, Germany) were introduced in a 30-fold molar excess relative to the level of anhydroglucose units in the HPMC. The mixture was vigorously stirred under nitrogen in the dark for three days at ambient temperature.

Perethylation was repeated with addition of a three-fold molar excess of sodium hydroxide and ethyl iodide (compared to the initial 30-fold addition). Stirring at room temperature was continued for an additional two days. Optionally, the reaction mixture could be diluted with up to 1.5 mL DMSO to ensure good mixing during the course of the reaction. Next, 5 mL of 5 % aqueous sodium thiosulfate solution was poured into the reaction mixture, which was then extracted three times with 4 mL of dichloromethane. The combined extracts were washed three times with 2 mL of water. The organic phase was dried with about 1 g anhydrous sodium sulfate. After filtration, the solvent was removed with a gentle stream of nitrogen, and the sample was stored at 4 °C until needed.

Hydrolysis of about 5 mg of the perethylated samples was performed under nitrogen in a 2-mL screw-cap vial with 1 mL of 90 % aqueous formic acid under stirring at 100 °C for 1 h. The formic acid was removed in a stream of nitrogen at 35–40 °C, and the hydrolysis was repeated with 1 mL of 2M aqueous trifluoroacetic acid for 3 h at 120 °C under an inert nitrogen atmosphere with stirring. After completion, the trifluoroacetic acid was removed to dryness in a stream of nitrogen at ambient temperature using about 1 mL of toluene for co-distillation.

The residues of the hydrolysis were reduced with 0.5 mL of 0.5M sodium borodeuteride in 2N aqueous ammonia solution (freshly prepared) for 3 h at room temperature with stirring. The excess reagent was destroyed by drop-wise addition of about 200 μL of concentrated acetic acid. The resulting solution was evaporated to dryness under a stream of nitrogen at about 35–40 °C and subsequently dried under vacuum for 15 min at room temperature. The viscous residue was dissolved in 0.5 mL of 15 % acetic acid in methanol and evaporated to dryness at room temperature. This process was repeated five times and then repeated four additional times with pure methanol. After the final evaporation, the sample was dried under vacuum overnight at room temperature.

The residue of the reduction was acetylated with 600 μL of acetic anhydride and 150 μL of pyridine for 3 h at 90 °C. After cooling, the sample vial was filled with toluene and evaporated to dryness under a stream of nitrogen at room temperature. The residue was dissolved in 4 mL of dichloromethane, poured into 2 mL of water, and extracted with 2 mL dichloromethane. The extraction was repeated three times. The combined extracts were washed three times with 4 mL of water and dried with anhydrous sodium sulfate. The dried dichloromethane extract was subsequently analyzed by gas chromatography (GC).

Depending upon the sensitivity of the GC system, a further dilution of the extract could be necessary. Gas-liquid chromatographic (GLC) analyses were performed with an Agilent 6890N (Agilent Technologies GmbH, Boeblingen, Germany) equipped with Agilent J&W capillary columns (DB5, 30 m, 0.25-mm ID, 0.25-μm phase layer thickness) operated with 1.5-bar helium carrier gas. The gas chromatograph was programmed with a temperature profile that held constant at 60 °C for 1 min, heated at a rate of 20 °C/min to 200 °C, heated further at a rate of 4 °C/min to 250 °C, then heated further at a rate of 20 °C/min to 310 °C, where it was held constant for another 10 min. The injector temperature was set to 280 °C, and the temperature of the flame ionization detector (FID) was set to 300 °C. Exactly 1 μL of each sample was injected in splitless mode at a 0.5-min valve time. Data were acquired and processed with a LabSystems Atlas work station (Thermo Scientific, Dreiech, Germany).

Quantitative monomer composition data were obtained from the peak areas measured by GLC with FID. Molar responses of the monomers were calculated in line with the effective carbon number (ECN) concept but modified as described in the table below. The ECN concept has been described by Ackman and Addison [37,38] and applied to the quantitative analysis of partially alkylated alditol acetates by Sweet et al. [39].

Increments used for ECN calculations.

Type of carbon atom	ECN increment
Hydrocarbon	100
Primary alcohol	55
Secondary alcohol	45

In order to correct for the different molar responses of the monomers, the peak areas were multiplied by molar response factors, which are defined as the response relative to the 2,3,6-tri-*O*-methylated monomer. Data provided are based on duplicate analysis of three independently prepared samples.

3. Results and discussion

3.1. Standard characterization of HPMC

Samples from twenty commercial batches of HPMC 2208 were used for this study. These HPMC batches were produced at commercial scale over a three-year time period. Several HPMC properties were analyzed for each batch and are listed in Table 1.

It should be noted that samples from most of the batches were randomly selected from inventory. Some of the samples, however, were specifically selected because those batches exhibited relative extremes in either HP substitution or 2 % viscosity compared to the other batches.

The compendial ranges of HPMC 2208 substitution are 19–24 % Me content and 4–12 % HP content. The commercial samples contained, on average, 23.0 ± 0.4 % Me content and 8.6 ± 0.3 % HP content. Because Me and HP substitution are both dependent on the average molecular weight of the glucose unit and therefore are not independent of each other, these values are often converted to degree of substitution (DS) and molar degree of substitution (MS), representing the number of substituents on one glucose unit. After conversion, the average values of DS (Me) and MS (HP) of the commercial samples were 1.45 ± 0.03 and 0.22 ± 0.01, respectively. This clearly shows the capability to produce HPMC 2208 (METHOCEL™ K4M) in a reproducible range of DS and MS, which is of highest importance for obtaining consistent CR performance.

Viscosity of HPMC has also been documented to impact CR performance (see Background section). Viscosity is primarily influenced by polymer chain length, where doubling chain length typically increases viscosity 10-fold. Hence, 2 % viscosity is a compendial proxy for HPMC

Table 1
Overview of quality analysis of the twenty commercial HPMC 2208 batches.

Commercial Batch No.	%Me	%HP	DS (Me)	MS (HP)	2 % Viscosity @ 20 °C (mPa·s)	50 % Cumulative Volume Particle Size (μm)	%NaCl
1	22.8	8.3	1.43	0.22	3711	93.8	0.2
2	23.1	8.7	1.46	0.23	4514	91.9	0.3
3	22.2	9.1	1.40	0.24	3638	84.3	0.3
4	22.6	8.4	1.42	0.22	4953	88.7	0.1
5	22.7	8.2	1.42	0.21	4015	94.1	0.2
6	23.0	8.5	1.45	0.22	4444	97.8	0.2
7	23.3	8.7	1.47	0.23	3506	102.1	0.3
8	23.2	8.8	1.47	0.23	3897	110.8	0.3
9	23.1	8.6	1.46	0.22	3615	109.1	0.3
10	23.1	8.6	1.46	0.22	3615	103.7	0.3
11	22.2	8.6	1.39	0.22	3756	96.7	0.6
12	23.0	8.8	1.45	0.23	3810	107.9	0.3
13	23.0	8.7	1.45	0.23	4325	103.1	0.4
14	23.3	8.7	1.47	0.23	3775	99.3	0.3
15	23.4	8.7	1.48	0.23	3849	99.3	0.3
16	22.9	8.5	1.44	0.22	4364	98.8	0.4
17	22.8	7.9	1.43	0.20	4562	101.9	0.3
18	23.6	8.4	1.49	0.22	4322	104.3	0.3
19	23.1	8.7	1.46	0.23	4057	101.2	0.4
20	23.0	8.7	1.45	0.23	3839	100.8	0.4
Average	**23.0**	**8.6**	**1.45**	**0.22**	**3996**	**99.2**	**0.3**
Standard deviation	0.4	0.3	0.03	0.01	414	6.6	0.1
Relative standard deviation (%)	1.5	3.0	1.8	3.2	10.4	6.7	36.5

molecular weight. HPMC is produced using cellulose pulp as raw material, so there is some inherent batch-to-batch variability in viscosity since pulp is a natural resource and varies in molecular weight. As can be seen in Table 1, average 2 % viscosity was 3996 ± 414 mPa·s.

Salt content and particle size are variables dependent upon the production process (washing and grinding). It is very important to control these variables and consistently produce the same level of quality. Salt content should be low to provide a pure HPMC, and the particle size distribution should be consistent to ensure reproducible flow properties and particle distribution throughout the matrix tablet. As can be seen in Table 1, the process was in control for all the commercial batches, with all parameters exhibiting only minor deviations. The increase of relative standard deviation regarding salt content was due to minor variation among already low salt content values and thus did not cause concern.

3.2. Characterization of granulations and tablets

3.2.1. Physical properties of granulations

The average compressibility index for the twenty corresponding granulations was 20 ± 3 %, indicating reproducible flow and compression properties. Average cumulative size values were 21 ± 3 % <63 μm and 61 ± 7 % <315 μm, reflecting reproducible granule size attributes.

3.2.2. Physical properties of tablets

Monolithic matrix tablets were compressed using a Kilian rotary press and varying compression force (22 kN–50 kN) in order to obtain consistent tablet hardness across all twenty batches. Weight and hardness targets were 500 mg and 90 N, respectively. Average tablet weight was 502 ± 3 mg, and average tablet hardness was 94 ± 8 N. Tablet weight variation for all twenty corresponding batches was below 1 %, indicating suitable granulation flow and die fill during tablet compaction.

3.2.3. Controlled release of paracetamol from matrix tablets

Paracetamol is one of most common over-the-counter APIs for treating pain and fever [40]. Leyk and Wesolowski could show no chemical reactions or hydrogen bonding between paracetamol and HPMC based on FT-IR and Raman characterization, but could show reduced crystallinity via DSC, which indicated some interactions between the molecules [41]. Pugliese and co-workers (Pugliese et al., 2021) used nuclear magnetic resonance (NMR) to identify these interactions. They used hypromellose acetate succinate (HPMCAS), a derivative of HPMC with low molecular weight for their study. At low paracetamol concentration (< 20 wt %), interactions between the aromatic protons of the API and the cellulose backbone could be identified. Furthermore, interactions were identified between the NH moiety on the paracetamol molecule and the proton of the HPMC-AS methyl substituent. These interactions play an important role to reduce crystallinity of the paracetamol and to stabilize the amorphous state, ultimately increasing bioavailability of the API, the overall goal of their study.

In our study, the paracetamol release profiles from matrix tablets produced using the twenty HPMC 2208 (METHOCEL™ K4M) materials are shown in Fig. 1. The dissolution testing methodology provided standard deviation of release data no more than 1.9 % at the 22 h timepoint for any particular n = 6 dissolution test, across all twenty sets of dissolution trials, so dissolution measurement variability was deemed sufficiently low to elucidate the slight change in paracetamol release observed during the latter portion of the twenty dissolution testing profiles shown in Fig. 1.

To assess comparability between the release profiles, f2 fit factors were calculated (Table 2). The f2 fit factor directly compares the difference between percent API dissolved per unit time for a test and reference formulation by approximating the percent error between two curves [42]. An f2 value of 100 means that test and reference are identical. An f2 value as low as 50 is still considered equivalent to the

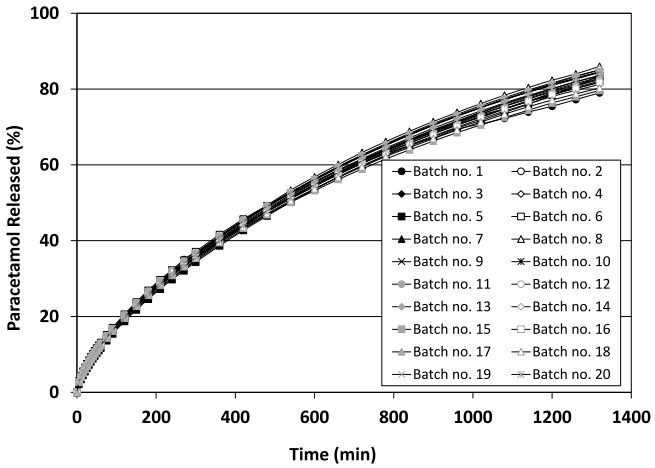

Fig. 1. Paracetamol release vs. time from the matrix tablets as a function of the commercial HPMC 2208 material used.

Table 2
F2 fit factors of nineteen of the twenty HPMC 2208 batches investigated.

Commercial Batch No.[a]	% API Released at $t = 22$ h (n = 6)	f2 fit factor at 22 h
2	82.7	86
3	82.9	87
4	81.2	90
5	83.6	86
6	82.1	89
7	85.1	78
8	86.0	75
9	84.4	77
10	83.5	83
11	81.8	90
12	85.1	79
13	83.1	85
14	82.5	87
15	84.6	79
16	81.8	90
17	79.6	94
18	80.3	95
19	84.4	79
20	83.6	83
Average	**83.1**	**85**
Standard deviation	1.7	5.8
Relative standard deviation (%)	2.0	6.9

[a] Commercial batch no. 1 was used as reference for calculating f2 fit factors.

reference. Tablets made with commercial HPMC 2208 batch no. 1 were used to generate the reference release profile for f2 fit factor calculations. Average f2 fit factor for all nineteen batches was 85 ± 6, indicating equivalence between all batches and only minor batch-to-batch variation. Paracetamol release at 22 h ranged from 79 to 86 % with an average value of 83.1 ± 1.7 %, exhibiting minimal deviation and affirming performance equivalence between all twenty batches. Even though paracetamol release was comparable across the 20 sets of matrix tablets, the discriminatory capability of the dissolution testing methodology did allow observation that the dissolution profiles began to slightly deviate towards the end of the dissolution testing timeframe.

To better understand release kinetics, paracetamol release data corresponding to each of the twenty HPMC batches were fit to the Korsmeyer-Peppas power law equation, $Q = kt^n$, where Q is the fraction of drug released at time t, k is a rate constant, and n is a diffusional exponent characteristic of the release mechanism [43,44]. Values for parameters k and n, obtained by nonlinear curve fitting of the paracetamol release data up to $t = 2$ h, are given in Table 3. API release data

Table 3
Nonlinear fits of API release to the Korsmeyer-Peppas power law equation, $Q = kt^n$.

Commercial Batch No.	% API Released at $t = 4$ h (n = 6)	k	n	r^2
1	32.0	14.21	0.567	0.9964
2	30.8	13.29	0.603	0.9984
3	30.3	13.02	0.608	0.9982
4	30.1	12.99	0.604	0.9985
5	29.7	12.58	0.617	0.9988
6	32.3	14.39	0.573	0.9980
7	31.7	13.70	0.602	0.9984
8	31.8	13.76	0.603	0.9985
9	31.5	13.63	0.601	0.9983
10	31.3	13.55	0.600	0.9983
11	32.1	13.52	0.593	0.9984
12	31.8	13.88	0.596	0.9986
13	31.1	13.51	0.599	0.9984
14	30.9	13.45	0.598	0.9984
15	31.9	13.83	0.596	0.9985
16	30.9	13.43	0.595	0.9984
17	30.9	13.57	0.582	0.9984
18	32.2	13.65	0.584	0.9983
19	31.5	13.61	0.602	0.9982
20	30.7	13.20	0.607	0.9987
Average	**31.3**	**13.54**	**0.596**	**0.9983**
Standard deviation	0.7	0.41	0.012	0.0005
Relative standard deviation (%)	2.3	3.0	2.0	0.05

from the monolithic matrix tablets fit the power law equation suitably, with r^2 correlations ≥ 0.996. Paracetamol release at 4 h is also given in Table 3. Across the twenty batches investigated, paracetamol release at 4 h ranged from 29.7 to 32.3 %, an expectedly narrow range of release at 4 h across the 20 sets of matrix tablets due to the fact that the 20 release profiles did not begin to deviate until the latter portion of the dissolution testing period.

From the twenty matrix tablet batches, n ranged from 0.57 to 0.62, reflecting consistent CR performance batch-to-batch. According to Ritger and Peppas [43,44], n should fall between 0.46 and 0.50 for purely Fickian diffusion-based release. It is not surprising that this matrix tablet formulation, based upon the higher values of n, only partially modulated release via diffusion. Paracetamol is a sparingly soluble API, and paracetamol release depended upon both diffusion through, and erosion of, the HPMC hydrogel layer that enveloped the matrix tablet.

3.3. Rheological characterization of HPMC

3.3.1. Powder dissolution temperature

CR performance occurs following formation of a swollen hydrogel layer of HPMC that envelops the matrix tablet once it is exposed to aqueous gastrointestinal fluid. How quickly this hydrogel layer forms depends upon the distribution of HPMC particles throughout the matrix tablet as well as the hydrophilic properties of HPMC and how readily the particles hydrate upon exposure to aqueous fluid. Resilience and erosion of the hydrogel layer depends upon the extent of entanglement of HPMC polymer chains. Doelker summarized various approaches to characterize cellulose ethers, such as solubility parameters, surface free-energy terms, and glass transition temperatures [45]. Sarkar et al. described the presence of various solution states for cellulose ethers depending upon substitution level and temperature. Solution calorimetry was described as a sensitive method to investigate exothermic heat of hydration of the cellulose ether, whereas dehydration was described as endothermic [46]. Joshi and Wilson reported the presence of endothermic and exothermic events during dissolution of HPMC E5 [47]. Further characterization of HPMC by thermal analysis was reviewed by Ford, and the advantages and disadvantages of the various methodologies were highlighted [48].

In the present paper, a new rheological technique is described to investigate the use of powder dissolution temperature (PDT) to relate HPMC hydration to CR performance. HPMC powders are insoluble in hot water and dissolve with decreasing temperature. The PDT measurement is performed with a rheometer using a cup-and-stirrer set-up. The HPMC powder is added at high temperature to the water, at which point it is insoluble. This suspension is continuously stirred at 300 rpm to ensure a homogenous distribution of the HPMC powder in hot water and to avoid sedimentation of undissolved particles. Due to this suspension characteristic only low torque values are investigated. The suspension is cooled down at 1 °C / min while stirring. At a characteristic temperature, the HPMC starts to dissolve. Initiation in HPMC dissolution is evidenced by a sharp increase in torque values over a narrow temperature range. Upon further cooling, a second slope of torque-temperature dependence is observed. In the range of the second slope, most of the HPMC powder is hydrated, and this smaller slope of torque-temperature dependence represents the increase in HPMC solution viscosity with decreasing temperature. Fig. 2 shows the premise of PDT at a concentration of 1.5 % HPMC in water.

A subset of torque vs. temperature data (covering a range of ~2.5 °C) from the first slope of the PDT profile, indicated in Fig. 2 within the circled portion, is built to highlight the largest magnitude slope. The midpoint of this temperature range is reported as temperature at inflection, indicated by the dotted arrow in Fig. 2. The slope of that linear fit is reported as the slope at inflection, and this linear slope is used to extrapolate back to the x-axis to obtain the onset powder dissolution temperature, or PDT, indicated by the dashed arrow in Fig. 2. The PDT values for all investigated batches were determined and are summarized in Table 4. Average PDT was 51.8 ± 0.8 °C, again confirming consistency of these commercial batches and indicating utility of this measurement as a metric for HPMC hydration.

3.3.2. Shear viscosity

Most cellulose derivatives in solution, and, in fact, most polymers in solution, exhibit a shear rate-dependent viscosity. Fig. 3 shows an example for shear rate-dependent viscosity of one HPMC solution at 2 % concentration in water at 20 °C. At low shear rate, viscosity is independent of shear. This viscosity is called the zero-shear viscosity. Both an increase in segment density with concentration and an increase in molar mass can lead to a rise in viscosity via an increase in intermolecular interactions. Above the critical shear rate, $\dot{\gamma}crit$ viscosity decreases with increasing shear. This region is called the non-Newtonian or power law region. Here, shear-thinning is caused by disentanglement of the polymer coils in solution or increased orientation of polymer coils in the direction of flow [49]. Further studies by Clasen et al. demonstrated

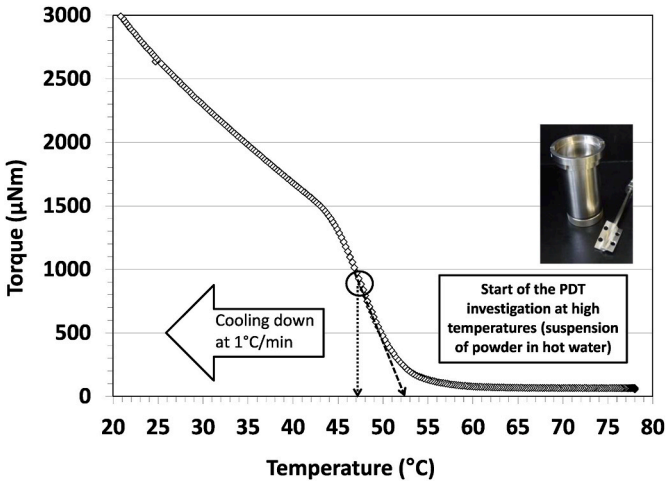

Fig. 2. Illustration of the powder dissolution temperature (PDT) principle of HPMC at a concentration of 1.5 % in water.

Table 4
Powder dissolution temperatures (PDTs) of samples from the twenty HPMC batches investigated.

Commercial Batch No.	Temperature at Inflection (°C)	PDT Slope @ Inflection (μNm/°C)	PDT (°C)
1	46.9	−181	51.5
2	47.9	−214	52.5
3	49.2	−142	53.8
4	48.0	−228	52.0
5	46.9	−190	51.8
6	48.1	−204	52.0
7	47.7	−188	51.9
8	48.2	−219	52.2
9	47.7	−192	51.9
10	47.9	−199	51.9
11	47.3	−203	52.0
12	48.6	−201	52.4
13	47.9	−233	51.6
14	47.8	−181	52.1
15	47.3	−208	51.6
16	46.7	−213	51.0
17	45.4	−230	49.6
18	46.2	−206	50.2
19	47.9	−208	51.8
20	47.7	−253	51.5
Average	**47.6**	**−204**	**51.8**
Standard deviation	0.8	23.5	0.8
Relative standard deviation (%)	1.8	11.5	1.6

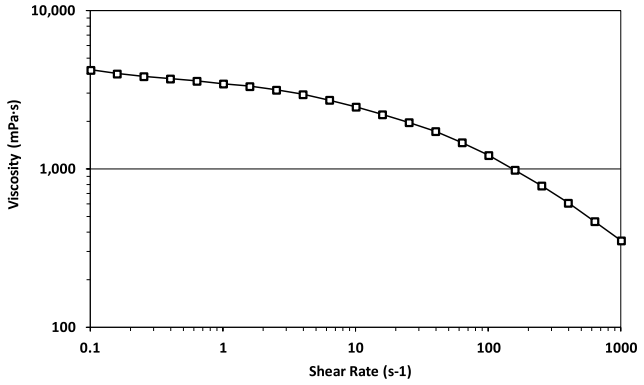

Fig. 3. Illustration of viscosity shear-rate dependence of HPMC at a concentration of 2 % in water at 20 °C.

that flow behavior of a moderately concentrated solution, without intermolecular interactions, is mainly driven by disentanglements of polymer coils [50]. Measured viscosities at a shear rate of 10 s^{-1} of all investigated batches are summarized in Table 5. Average zero-shear viscosity was 2695 ± 296.9 mPa·s.

3.3.3. Gelation temperature

Besides the viscosity enhancing properties of HPMC, these macromolecules are also known for their thermo-reversible precipitation and gelation performance upon heating [51]. These thermo-dependent properties can be further refined to two characteristic temperatures: a lower critical solution temperature (LCST), where the polymer solution exhibits clouding or precipitation, and a gelation temperature (T_{Gel}), where the polymer solution exhibits a sol-gel transition. We focused on gelation temperature in our investigation. Table 5 lists gelation temperatures for the twenty commercial HPMC batches. Onset gelation temperature was 76.1 ± 0.8 °C; gelation temperature was 78.6 ± 0.9 °C.

In the opaque temperature region, we have found that the solutions do not phase separate and remain uniformly opaque up to several weeks. These observations indicate strong coupling between phase separation

Table 5
Onset gelation temperature and gelation temperature properties measured for the twenty HPMC materials investigated.

Commercial Batch No.	Viscosity [20 °C] at 10 s^{-1} (mPa·s)	Onset Gelation Temperature (G'min) (°C)	Gelation Temperature (Crossover of G′ and G″) (°C)
1	2590	76.0	79.0
2	2840	75.2	77.5
3	2130	75.7	78.2
4	3100	76.7	78.0
5	2630	75.5	77.0
6	3080	75.0	77.0
7	2440	75.7	79.2
8	2610	77.0	78.5
9	2470	76.0	77.5
10	2310	74.5	78.7
11	2360	75.7	79.0
12	2580	76.0	79.7
13	3190	77.0	80.0
14	2620	75.7	79.0
15	2510	76.5	79.2
16	2910	76.7	79.0
17	3190	77.7	79.2
18	2690	75.7	78.5
19	2810	76.2	78.2
20	2840	77.2	80.2
Average	**2695**	**76.1**	**78.6**
Standard deviation	296.9	0.8	0.9
Relative standard deviation (%)	11.0	1.0	1.2

and gelation [52]. The study and understanding of the process is complex due to the possibility of several different phenomena occurring during thermo-induced phase transition of the HPMC solution [52–57]. It is widely accepted that hydrophobic interactions are the main driving force for gelation [58]. Furthermore the role of inter-chain hydrogen bonding in gelation continues to be discussed and debated [59].

The thermal transition process is further strongly influenced by the content of hydrophilic and hydrophobic functional groups in the macromolecule [51,60]. Thermo-rheology has been used previously to study thermal transition of HPMC solutions [61]. These approaches were used in our study to analyze characteristics of the HPMC samples with respect to their thermo-dependent properties. Fig. 4 illustrates an example for the temperature dependence of storage modulus G′ and loss modulus G″ of one HPMC solution at a concentration of 2 %. Measurement conditions were chosen according to the linear visco-elastic region of the material and to achieve suitable signal-to-noise ratio, but also to avoid destruction of aggregates or associates during gelation. Only the G′

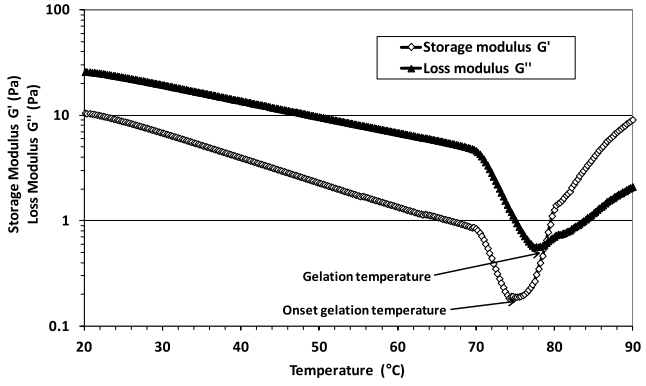

Fig. 4. Illustration of temperature dependence of the storage modulus G′ and the loss modulus G″ of an HPMC solution at a concentration of 2 % in water.

and G″ curves of one of the samples are shown in Fig. 4, because there were only minimal batch-to-batch differences observed between the twenty HPMC materials investigated.

The storage and loss moduli represent elastic properties and viscous properties, respectively, of the material at a given temperature. Temperature dependence of the storage modulus, G′, and loss modulus, G″, can be separated into three zones. At low temperature, the viscous properties are dominant in comparison to the elastic properties. This represents the typical attributes of a viscous fluid with entanglements between the polymer chains in solution [62]. With increasing temperature, Brownian motions of the polymer molecules increase, and thermodynamic solvent quality decreases. Therefore, the moduli decrease.

As also described by Sarkar, analysis of temperature dependence of the moduli exhibits two inflection points. The sharp decreases in G′ and G″ presumably indicate precipitation of certain fractions of the HPMC macromolecules. Upon further increase in temperature, the solutions begin to gel when G′ begins to increase sharply [63]. According to Winter et al. the exact gelation points are represented by the independent crossover of G′ and G″ as a function of frequency [64]. Sarkar describes the gelation point as the minimum of the G′ values, which is consistently a few degrees below the crossover temperature of G′ and G″ [63].

3.4. Chemical structure analysis of HPMC

Detailed knowledge of the chemical structure of a complex composition like HPMC (Fig. 5) is key to understanding the performance attributes of cellulose ethers and the potential influence of batch-to-batch variation. HPMC is produced in a polymer-analogue reaction using cellulose pulp as raw material, so a variety of substituted polymer chains are created. No two single polymer chains are substituted with methyl or hydroxypropyl groups in the same way.

When analyzing the chemical structure of a cellulose ether, various hierarchical levels of substituent distribution must be taken into account. The repeating unit of the raw material is glucose. Three hydroxyl groups of each glucose unit (positions 2, 3, and 6) can be substituted during etherification. Therefore, one level of chemical structure is the substituent distribution of methyl and hydroxypropyl groups within the glucose unit. The next level focuses on distribution of substituents along the polymer chain, indicating the presence or absence of higher and lower substituted regions. The highest level currently discussed in the literature is the heterogeneity along several polymer chains. The research presented in the current paper focuses on substituent distribution within the glucose units.

Methylation and hydroxypropylation are performed simultaneously. Therefore, each of the three hydroxyl groups of a glucose unit can be substituted with a methyl, hydroxypropyl, methylhydroxypropyl (capped), or multiple hydroxypropyl groups linked to each other (tandem reaction groups). In theory, $4^3 = 64$ different substituted glucose units can be generated, not taking further tandem reactions into account.

If process variations occur, the kinetics of each of these etherifications can change, and modifications in substituent distribution might subsequently be obtained. Therefore, it is important to verify reproducibility of the chemical composition of HPMC. Methodologies to analyze substituent distributions within the monomer units of nonionic cellulose ethers have been previously published [65–69]. The method we used has recently been modified for industry [70], as described in the Experimental section.

Fig. 6 shows molar fractions of the un- (c0), mono- (c1), di- (c2), and tri- (c3) methylated glucose units of the twenty HPMC materials.

Several models have been published that compare the experimentally determined distribution of methyl groups with a calculated distribution. The gray curves in Fig. 6 are plotted according to Spurlin's model [71] using a relative reactive rate constant k2 : k3 : k6 of 1 : 1 : 1 and are used to show how the ideal molar fraction of c0 – c3 varies as DS values are varied between 0 and 3. It has been previously reported that Reuben's model [72] is most suitable for comparing a single sample to a predicted substituent distribution of methyl groups as it takes into account increased reactivity of the position 3 –OH group if position 2 is already substituted. However, Spurlin's model was preferred in our study in order to compare a large sample set with calculated ideal values. The focus of this discussion is not the accuracy of the model, but rather to show the extent of ideal c0 – c3 variation as a function of DS.

As observed in Fig. 6, the twenty HPMC materials were all very similar in both DS and chemical structure values. For the present analysis, DS (%HP) was equivalent to MS (%HP). This does not mean that no tandem HP reaction products were present in these samples. Rather, it means that the tandem groups were not detectable with the applied gas chromatographic approach. The glucose units with a side chain of two linked HP groups were present, but to a very low extent; and because they were chromatographically separated based on their different methyl patterns, they could not be detected using the described methodology. A different approach is described in the literature [66] that uses, in addition to the present method, an alternative permethylation method as the first step in sample preparation. Consequently, all groups containing, for example, two tandem HP groups on position 2 are then grouped into one signal. Accuracy of the MS (%HP) analysis increases, but the information content of methyl distribution is lost.

For all data points throughout the chemical structure analysis, it can be concluded that the twenty commercial HPMC samples reflected very minimal batch-to-batch variation in substituent distribution.

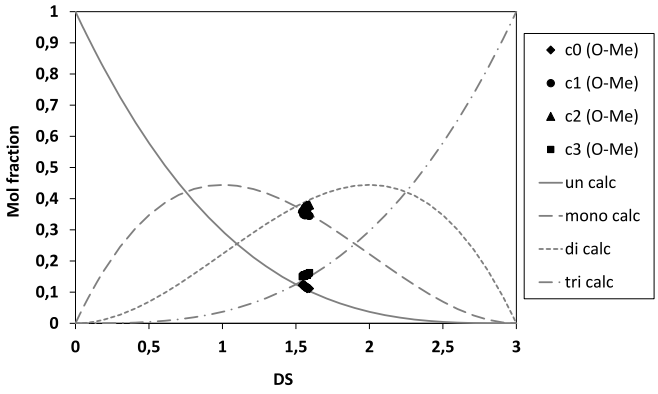

Fig. 6. Comparison of chemical structure analysis of the twenty HPMC 2208 (METHOCEL™ K4M) materials studied.

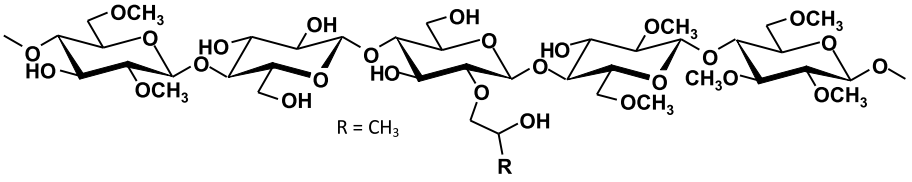

Fig. 5. Example of an HPMC structure with a DS of ~1.4 and an MS of ~0.2.

3.5. Analysis of relationships: HPMC FRCs, rheology, and CR performance

The main objective of the study was to investigate the impact of batch-to-batch variation between twenty commercial HPMC batches upon CR performance. Table 6 provides a summary of various material attributes studied. Batch-to-batch variations in material attributes were very small with respect to standard quality, rheology, chemical structure, and corresponding tablet physical properties and CR performance.

Another key objective was to define and understand the HPMC key FRCs impacting CR performance. A main effects model was constructed using the FRCs of the twenty HPMC materials and the corresponding CR performance data from matrix tablets containing those twenty HPMC materials. In this way, a first-impression rank-ordering of FRCs affecting performance could be obtained for these HPMC materials in this formulation.

The overall *p*-value for the main effects model was significant ($p < 0.05$), indicating that there was at least one significant regression factor. The FRCs were ranked from highest to lowest in the following order of impact on paracetamol release from this matrix tablet formulation at 22 h: %HP > 2 % viscosity > D50 particle size > %Me. Below are the *p*-values associated with each of the regression factors.

FRC	*p*-value
%HP	<0.05
2 % viscosity	0.06
D50 particle size	0.13
%Me	0.75

HP substitution significantly impacted controlled release of paracetamol from this matrix tablet formulation. Technically, 2 % viscosity was not a significant factor in our model ($p > 0.05$), but its *p*-value of 0.06 was sufficiently low to justify further evaluation alongside HP substitution. In this study 20 commercial batches of HPMC 2208 (METHOCEL™ K4M) were used with particle size distributions in a very narrow range and therefore no impact of this parameters was also expected.

Accordingly, the strongest driver for the paracetamol release at 22 h are shown in Fig. 7 based on the HP substitution and the 2 % viscosity. Direct correlation was observed between %HP substitution and paracetamol release; paracetamol release increased as %HP substitution increased. The ellipses depict 95 % confidence intervals.

An indirect correlation was observed between 2 % viscosity and paracetamol release; paracetamol release decreased as 2 % viscosity of the respective HPMC batch increased. Along with the broader scatter in data, the broader 95 % confidence interval for paracetamol release as a function of 2 % viscosity vs. that observed for paracetamol release as a function of %HP substitution is consistent with the rank-ordered *p*-values.

Although a direct and significant correlation was found between HP substitution and paracetamol release at 22 h, CR performance was overall consistent from batch-to-batch. Paracetamol release at 22 h only varied from 79 to 86 % across a %HP substitution range of 7.9 – 9.1 % (MS 0.20 – 0.24), i.e., minimal HPMC batch-to-batch variability resulted in minimal variability in CR performance. As mentioned earlier, samples from the twenty commercial HPMC 2208 (METHOCEL™ K4M) batches were selected over a three-year production period in order to capture materials representative of typical %HP and 2 % viscosity production ranges. Samples from most of the batches were randomly selected. Some of the samples, however, were specifically selected because those batches exhibited relative extremes in either %HP substitution or 2 % viscosity compared to the other batches in inventory. Therefore, batch-to-batch variabilities in these two FRCs are representative of what is typically manufactured.

Another objective was to investigate rheological performance as a research tool for predicting CR performance. A number of rheological performance attributes of HPMC 2208 (METHOCEL™ K4M) were characterized, including powder dissolution temperature (PDT), shear rate dependent viscosity, onset gelation temperature, and gelation temperature. Of those rheological metrics, PDT exhibited the most promising predictability of paracetamol release.

A side-by-side comparison of paracetamol release, PDT, and %HP substitution was subsequently conducted and is shown in Fig. 8. Both paracetamol release and PDT correlated directly with %HP substitution. As shown in Fig. 8c, the correlation between paracetamol release and PDT was not as strong as the corresponding correlation between paracetamol release and %HP substitution. Nevertheless, there was a strong correlation between PDT and %HP substitution. This indicates that the PDT method could be a potential screening tool to predict CR performance. However, additional exploration is needed to gauge how predictive a potential screening tool PDT could be.

4. Conclusions

The objectives of this study were to investigate batch-to-batch variation of twenty commercial HPMC 2208 (METHOCEL™ K4M) materials produced over a three-year period on controlled release (CR)

Table 6
Summary of attributes for twenty commercial HPMC batches and corresponding granulation and tablet properties.

Characteristic	Average	Standard Deviation	Relative Standard Deviation (%)
Standard Quality Tests for HPMC			
%Me[a]	23.0	0.4	1.5
%HP[a]	8.6	0.3	3.0
DS(Me)	1.45	0.03	1.8
MS(HP)	0.22	0.01	3.2
2 % Viscosity @ 20 °C (mPa-s)[a]	3996	414	10.4
50 % Cum. vol. part. size (μm)[a]	99.2	6.6	6.7
NaCl (%)	0.30	0.11	36.5
Granulation Properties			
Compressibility index (%)	20	3	–
Granule size	21 % < 63 μm 61 % < 315 μm	3 % < 63 μm 7 % < 315 μm	–
Tablet Properties			
Tablet weight (mg)	502	3	0.6
Tablet hardness (N)	94	8	8.5
Paracetamol release @ 22 h (%)	83.1	1.7	2.0
f2 fit factor	84.8	5.8	6.9
Paracetamol release @ 4 h (%)	31.3	0.7	2.3
Nonlinear fit *k*	13.54	0.41	3.0
Nonlinear fit *n*	0.597	0.012	2.0
Nonlinear fit r^2	0.9712	0.0012	0.1
HPMC Rheological Properties			
Powder dissolution temp. @ inflection (°C)	47.6	0.8	1.8
Powder dissolution slope @ inflection (μNm/°C)	−204.7	23.5	11.5
Powder dissolution temp. (PDT, °C)	51.8	0.8	1.6
Shear viscosity @ 20 °C, 10 s^{-1} (mPa-s)	2695	297	11.0
Onset gelation temperature (°C)	76.1	0.8	1.0
Gelation temperature (°C)	78.6	0.9	1.2
HPMC Chemical Structure Analysis			
Chemical structure variables	RSDs ranged from 0.78 to 9.31 %		

[a] Functionality-related characteristics.

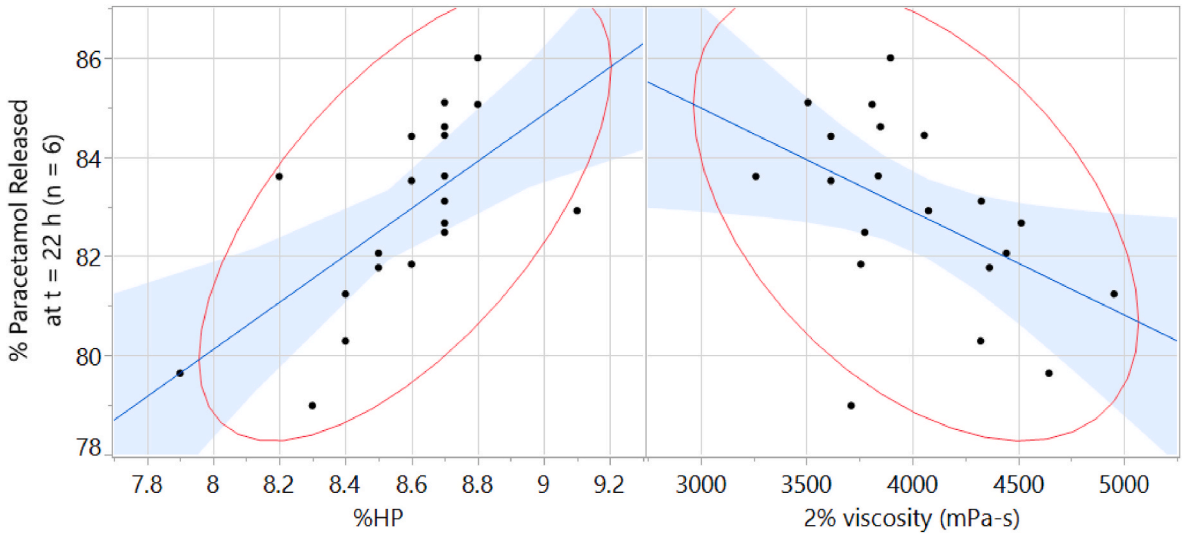

Fig. 7. Paracetamol release as a function of %HP content and 2 % viscosity.

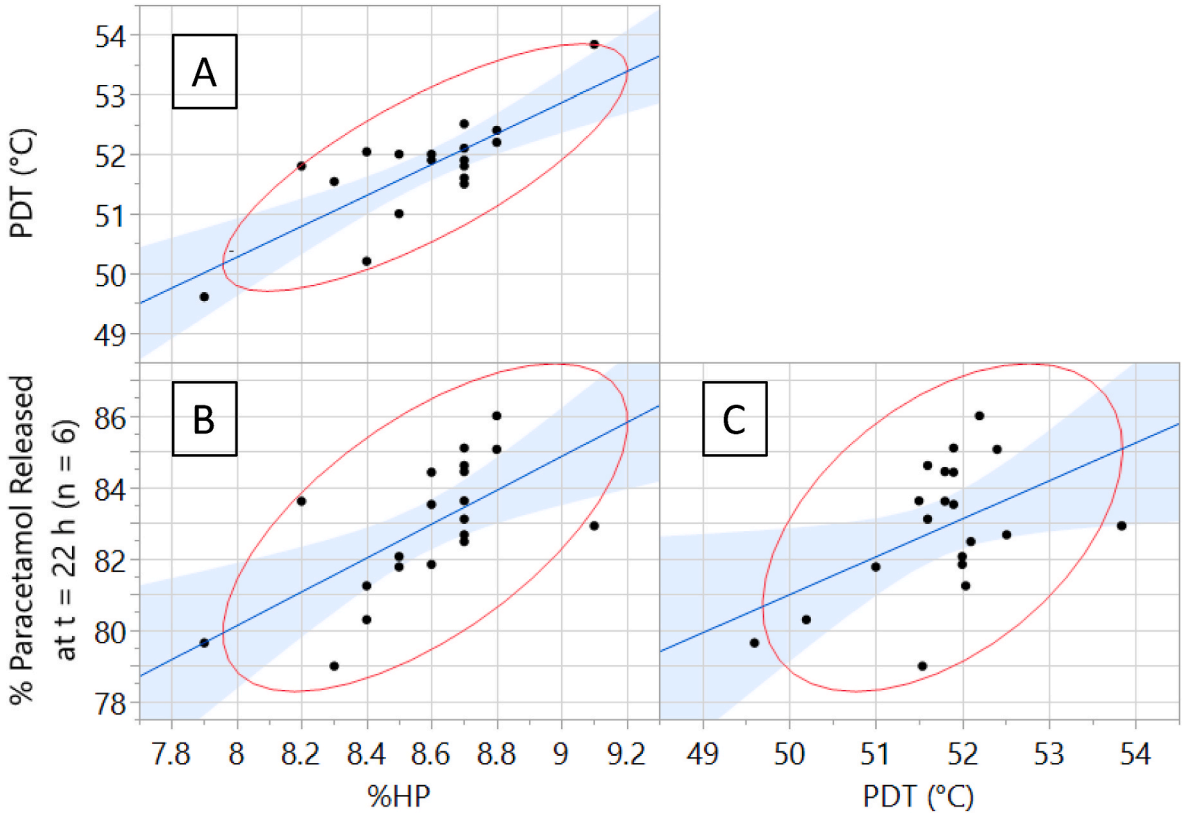

Fig. 8. Direct correlations observed between paracetamol release, PDT, and %HP content.

performance of paracetamol as model API and to introduce a new rheological performance attribute as a prediction tool for CR performance. HP substitution, in particular, was found to be the main driver impacting CR performance, followed by 2 % viscosity. Particle size and MeO substitution did not significantly impact matrix performance within the ranges investigated. Paracetamol release increased with increasing %HP substitution. The trend occurred, however, over a narrow API release performance range. Hence, the twenty commercial HPMC materials produced matrix tablets exhibiting reproducible batch-to-batch CR performance due to the fact that HPMC batch-to-batch variation was minimal. Testing the hypothesis of HP substitution as the main driver for CR performance within a particular viscosity range will be presented in a follow-up paper, where HPMC materials were synthesized at pilot plant scale covering a broader range of %HP substitution. This manuscript is currently in progress.

Powder dissolution temperature (PDT) was identified to be a promising indicator of CR performance. Like API release, PDT increased with increasing %HP substitution. Both matrix performance and rheological performance demonstrated that, within the typical batch-to-batch variation in FRCs, HPMC 2208 provides reproducible performance. PDT could be used as a rapid screening tool to approximate how a particular HPMC batch would modulate API release from a matrix

tablet. The strength of this correlation will be tested based on the data to be presented in the 2nd manuscript in progress.

CRediT authorship contribution statement

Matthias Knarr: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **True L. Rogers:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Oliver Petermann:** Writing – original draft, Resources, Investigation, Formal analysis, Conceptualization. **Roland Adden:** Writing – original draft, Visualization, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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