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Characterization of physicochemical properties of hydroxypropyl methylcellulose (HPMC) type 2208 and their influence on prolonged drug release from matrix tablets

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ABSTRACT

The key physicochemical properties of functional excipients should be identified, and the influence of their variability on the properties of the final dosage form should be evaluated during the development phase. Excipients produced by different manufacturers and/or by different manufacturing processes should have comparable properties. Hydroxypropyl methylcellulose (HPMC) with a high molecular weight is a functional excipient often used in solid matrix systems with prolonged release of active pharmaceutical ingredients (API). This study investigates whether HPMC manufactured by two manufacturers using different chemical procedures differs in particle-size distribution, particle shape, particle morphology, chemical composition, and dissolution of diclofenac sodium as a model drug. NIR spectroscopy was introduced and calibration models were developed to detect physical differences among HPMC batches from two different origins. The physical differences between HPMC samples were additionally confirmed with scanning electron microscopy (SEM), gas chromatography (GC) measurements, and dissolution testing of hydrophilic matrix tablets. Our results prove that, even if HPMC polymers manufactured from two different sources comply with the pharmacopeial specification, they significantly differ in physicochemical properties and thus influence the properties of the formulated dosage forms.

1. Introduction

Hypromellose, hydroxypropyl methylcellulose (HPMC) with a molecular weight ranging from 10,000 to 1,500,000, is one of the most frequently used polymers for the preparation of hydrophilic matrix tablets with prolonged release of active pharmaceutical ingredients (API). There are many reasons for the popularity of HPMC as an excipient: it is nontoxic, easy to handle, relatively cheap, easy to compact, and able to accommodate high levels of drug loading; moreover, the process variables show little effect on drug release [1]. Commercial HPMC is available in different viscosity (polymerization) and substitution grades with specifications included in United States (USP) and European (Ph. Eur.) pharmacopeia. The pharmacopeial specifications are broad and provide only average values of the polymer quality with respect to polymerization and substitution parameters. HPMC used as a pharmaceutical excipient is typically prepared by batch processes; that is, discrete quantities of powder are produced according to standard procedures rather than on a continuous basis [2]. Production begins with starting material of natural origin (i.e., wood or cotton). Minor batch-to-batch differences in the polymer manufacturing conditions can result in variation in the physical properties of the product. These batch variations are generally small, but if a formulation is not robust enough, or if batch variation is large, this could lead to a product that does not meet required specifications. Another source of variability of polymer properties and its functionality could be the raw materials from which HPMC is produced [2,3]. There are two major suppliers of pharmaceutical-quality HPMC that use different manufacturing procedures and raw materials, even though HPMC of the same grade from both manufacturers complies with the same pharmacopoeial monographs. Batch-to-batch variations within HPMC grades have also previously been reported [4–6].

The factors influencing drug release from hydrophilic matrix systems include viscosity and particle-size distribution of the polymer, ratio of the polymer to drug, polymer grade or use of mixtures of HPMC of different grades, compression pressure, thickness of the tablet, particle size of the drug, entrapped air in the tablets, molecular size of the drug, molecular geometry of the drug, solubility of the drug, the presence of excipients, and the mode of incorporation of these substances [7,8]. Polymer particle size is one of the

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polymer properties that has been indicated as responsible for the rate of polymer hydration. It has been claimed that small (fine) particle size ensures more rapid hydration and also gives rise to a more continuous gel layer formation. On the other hand, coarse fractions hydrate too slowly to form a fast-growing and continuous gel layer, and therefore excessively rapid initial release is more expressed [9,10].

NIR spectroscopy was found to offer many possibilities for industrial analytical applications. This is a very fast technique because spectra can be recorded in only a few seconds. The most interesting advantage of the technique is the non-destructive character of the analysis and its simplicity because a sample can be analyzed either without preparation or with only minimal sample preparation. In the pharmaceutical industry NIR has been successfully used for material identification, determining endpoints during powder mixing, moisture determination, tablet assay and crushing strength determination, predicting dissolution from tablets, determining moisture in lyophilized products through the bases of vials, detecting various polymorphic forms of the same compound, and particle-size determination [11–15]. Generally, NIRs and chemometrics are used to classify or quantify samples with regard to reference measurements [15]. It is well known that particle size affects the characteristics of NIR diffuse reflection spectra. Particle-size measurements with NIR spectroscopy have been reported and various chemometric approaches have been suggested for correlating particle size with NIR spectra [13]. One reference method for linking particle-size distribution with NIR spectra is laser diffraction. This method is also rapid, requires a small sample volume, provides information about particle-size distribution, does not need external calibration, shows high reproducibility, and can be performed in wet and dry conditions [16].

This study demonstrates how various commonly used characterization techniques (i.e., particle size analysis, NIR spectroscopic method in combination with multivariate data analysis, gas chromatography (GC) and scanning electron microscopy (SEM)) can be used to extend the quality control of incoming batches of HPMC raw material and how the differences correlate with the dissolution profiles from the final drug product. For this purpose, seven HPMC batches from two widely used sources were investigated: Methocel and Metolose. Although all the HPMC batches investigated have similar pharmacopeial specifications, the intention was to determine whether there are physicochemical differences between HPMC batches from the same source and from two different sources.

2. Materials and methods

2.1. Materials

Seven HPMC batches of the same substitution (USP type 2208) and viscosity grade (the nominal viscosity of 2% aqueous solution is 4000 mPa s) were used in the study. All of the samples used and their characteristics are listed in Table 1. HPMC batches were produced by Dow (Dow Chemical Co., USA) and Shin-Etsu (Shin-Etsu Chemical Co., Ltd., Tokyo, Japan).

Table 1
HPMC batches and viscosity of 2% (w/w) solutions in mPa s. All samples were USP 2208 substituent grade. Data were obtained by suppliers.

HPMC batches	Manufacturer	Viscosity (2% w/w) (mPa s)
A (Metolose)	Shin-Etsu Chemical Co., Ltd.	3940
B (Metolose)	Shin-Etsu Chemical Co., Ltd.	4140
C (Metolose)	Shin-Etsu Chemical Co., Ltd.	3740
D (Methocel)	Dow Chemical Co.	3580
E (Methocel)	Dow Chemical Co.	4386
F (Metolose)	Shin-Etsu Chemical Co., Ltd.	3630
G (Methocel)	Dow Chemical Co.	4124

2.2. Sieving of different HPMC batches

HPMC batches were mechanically sieved to selected particle-size fractions. An AS200 Digit Retsch (Japan) vibrational sieving apparatus was used. Thirty grams of each HPMC sample was passed through eleven sieves: 200 μm, 180 μm, 150 μm, 125 μm, 100 μm, 75 μm, 71 μm, 63 μm, 53 μm, 45 μm, and 32 μm. Sieving was carried out under ambient humidity and temperature. The agitation time was 20 min.

Twelve sieved fractions of HPMC batches from A to E were used as calibration samples and sieved fractions of HPMC-F and HPMC-G were subjected to the NIR models to prove its prediction ability.

2.3. Determination of particle-size distribution by laser diffraction as a reference method

Laser diffraction analysis was used as a reference method to determine particle-size distribution. Laser diffraction measurements were performed using a Mastersizer S (Malvern Instruments, UK). The instrument was equipped with a wet dispersion module with a stirrer (1500 rpm) to homogenize samples before measurements. Approximately 300 mg of each HPMC fraction was dispersed in 150 ml of anhydrous ethanol, where HPMC is practically insoluble. The results of each HPMC fraction was based on the volume-weight mean diameter $D(4,3)$, where each result was an average of three consecutive measurements.

2.4. Degree of substitution of HPMC batches investigated

The degree of substitution of all HPMC batches investigated was determined according to the Ph. Eur. procedure. The degree of substitution was determined after reaction with hydroiodic acid with an Agilent 6890, GC 4 apparatus equipped with a thermal conductivity detector. The carrier gas was helium for chromatography with a flow rate of 2 ml/min. The length of the column used was 1.8 m and its temperature was 100 °C. The column was filled with a stationary phase: diatomaceous earth for gas chromatography impregnated with 20% of poly(dimethyl)(75)(diphenyl)(25) siloxan. Adipic acid, isopropyl iodide, methyl iodide, and octane were used as reference solutions.

2.5. Recording of NIR spectra and development of calibration models

NIR reflectance spectra were measured using a fully calibrated multipurpose analyzer (MPA®) Fourier transform near-infrared spectrometer (Bruker Optics, Germany), which was equipped with an indium gallium arsenide (InGaAs) detector. The spectrum of each sample (the average of 32 scans) was recorded in triplicate with a resolution of 8 cm^{-1}. Bruker OPUS software (version 6.5) was used for all data collection and data analysis, in which the Optimizer function was used to obtain the optimal PLS models with optimal selection of the preprocessing technique and wavelength regions. All HPMC fractions were directly measured after sieving (no sample preparation was needed) using the diffuse reflectance mode by placing the powdered samples in glass vials and using a ceramic plate as reference. Sieved HPMC fractions of different batches and of two different origins were used in cross validation to build partial least squares (PLS) models. In PLS, calibration involves correlating the data in the spectral matrix X with the data in the matrix Y, representing the particle size of the analyte. The calibration function b correlates to property Y (the property of the analyte) of a