Carbohydrate Polymers 83 (2011) 843–851

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Ultrasonic degradation for molecular weight reduction of pharmaceutical cellulose ethers

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ARTICLE INFO

Article history:
Received 11 April 2010
Received in revised form 14 July 2010
Accepted 26 August 2010
Available online 29 September 2010

Keywords:
Cellulose ether
Pharmaceutical excipients
Molecular weight characterisation

ABSTRACT

Several pharmaceutical grade cellulose ethers, hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC) and ethylhydroxyethyl cellulose (EHEC) have been degraded to different molecular weights by exposing either a 1.5 or 4.0 wt.% aqueous solution of the polymer to varying periods of ultrasonic radiation over 24 h. The resulting solutions were characterised with respect to molecular weight and molecular weight distribution of the polymer using capillary viscometry, size exclusion (SEC) and in the case of HPC, dynamic and static light scattering. Depending upon the ultrasonication time, a range of polymer solutions were produced over a range of molecular weights in a suitable form for further experimental use. In all cases a limiting polymer molecular weight was reached after 24 h of ultrasonic degradation; the limiting polymer molecular weight was dependent upon the nature of the polymer and not the concentration of the polymer solution. From measurements of intrinsic viscosity using capillary viscometry and molecular weight using static light scattering, the Mark-Houwink parameters of HPC were found to be $K = 6.25 \times 10^{-5}$ and $a = 0.84$ over the molecular weight range 139,000–58,000 relative molecular mass.

1. Introduction

Cellulose is a linear homopolymer polysaccharide consisting of D-anhydroglucopyranose units joined together by β-1,4-glycosidic bonds. As a consequence of the extensive intramolecular hydrogen bonding present in cellulose, i.e. between the hydroxyl groups in position 3 and the ring oxygen atoms of the neighbouring glucose molecules and between the 6-hydroxyl groups and the oxygen bonds of the glycosidic linkages, it is insoluble in both hot and cold water. Etherification of the hydroxyl groups of cellulose produces water-soluble derivatives by liberating the hydrophilic nature of the hydroxyl groups resulting in the production of cellulose ethers (CEs) such as hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC) (now termed hypromellose), hydroxylethyl cellulose (HEC) and ethylhydroxyethyl cellulose (EHEC). CEs thus possess a greatly enhanced water solubility compared to the parent cellulose molecule and as such find use in a wide range of industries, for example the construction, ceramic, plastic, food, textile and pharmaceutical industry (Clasen & Kulicke, 2001). In particular, CEs are increasingly important in the formulation of solid, liquid, semi-solid and controlled-release formulations (Guo, Skinner, Harcum, & Barnum, 1998) since they are biocompatible and many possess 'generally regarded as safe' (GRAS) status (El Ghzaoui, Trompette, Cassanas, Bardet, & Fabregue, 2001; Li, He, Parthiban, Yin, & Serajuddin, 2005; Momcilovic, Schagerlöf, Wittgren, Wahlund, & Brinkmalm, 2005; Rowe, Sheskey, & Weller, 2003).

Examples of typical uses of CEs in pharmaceutical formulations include matrices in controlled-release drug delivery systems, binding agents during granulation, film formation during tablet coating, suspending agents for suspensions, steric stabilisers for colloids and thickening agents for creams and ointments (Guo et al., 1998; Li & Mei, 2006). Considering the list of classic applications associated with CEs, it is not surprising that medium and high viscosity grades tend to be more popular (Pfefferkorn, Beister, Hild, Thielking, & Kulicke, 2003).

In order to carry out investigations into the effect of polymer molecular weight on the performance of a formulation or process, it is necessary to obtain polymer samples with a range of molecular weights. For example, such studies include the effect of polymer molecular weight on suspension stabilisation (Duro et al., 1998) the effect of CE binder molecular weight on wet granulation (Parker, York, & Rowe, 1991) and molecular weight studies of HPMC used in the film coating of tablets (Rowe, 1980). However, the molecular weight range of interest may not always match with what is available commercially, and there is no guarantee that different grades

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0144-8617/$ – see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.carbpol.2010.08.068

of commercially available polymers are suitable for such studies, for example, Dahl, Calderwood, Bormeth, Trimble, and Piepmeier (1990) report significant batch-to-batch variability even from same viscosity specification polymers.

In addition to the need for polymers with a tailored molecular weight range there may be wider applications for using ultra-low molecular weight CEs in pharmaceutical formulations. For example, Lusvardi, Harcum, Skinner, and Durig (2003) report increased tablet strength, decreased friability and the formation of viable tablets over wider compression forces when lower molecular weight HPC is used as a binder for wet granulation. Due to the high expenditure associated with registering new excipients with regulatory agencies, using existing excipients for wider applications has clear advantages (Müller & Keck, 2004). Polymers are somewhat adaptable in this respect since the physical, rheological and mechanical properties of the material can typically be altered by changing the chain length or molecular weight of the polymer (Keary, 2001).

Of particular relevance to the present study is the use of hydrophilic polymers, such as HMPC, to produce nanoparticles of hydrophobic drug via wet bead milling (Goodwin, 2006; Sepassi et al., 2007). When preparing these polymer-coated nanoparticles using the limited molecular weight range of HPMC commercially available, it was noticed that stable nanoparticles were produced more rapidly and over a wider range of polymer concentrations when the lower molecular weight polymers were used. This was an important observation because solutions of higher molecular weight polymer tended to gel at the concentrations required for the wet bead milling.

One possible solution to providing both a source of low molecular weight polymers and a range of molecular weights is to degrade a polymer sample. Polymer degradation can be frequently carried out by chemical, thermal, enzymatic or mechanical methods (Clasen & Kulicke, 2001). Chemical methods have included the use of hydrogen peroxide to afford oxidative degradation (Pfefferkorn et al., 2003) as well as alkali or acid-mediated degradation, whereas enzymatic molecular weight reduction has been demonstrated by Wirick (1968) for a range of CEs using cellulases. Thermal and mechanical methods have the advantage of not requiring additional substances to be added to the polymer which eliminates the need for subsequent purification processes. However, chemical and thermal methods are random processes that lead to unwanted mono and oligomers (Kulicke, Clasen, & Lohman, 2005). Ultrasonic degradation is an established technique for the degradation of polymer molecules in solution (Schittenhelm & Kulicke, 2000) as it possesses several important advantages in that the polymer breaks towards the middle of the chain, no monomers are formed during the degradation and no side reactions take place (Kulicke et al., 2005).

Characterisation of polymer molecular weight of CEs marketed to the pharmaceutical industry is customarily limited to a single point viscosity determination, typically of a 2% (w/w) solution at 25 °C. For many of the applications of CEs, listed above, a viscosity specification has often proven adequate. However, with the implementation of Quality by Design approaches, it becomes necessary to understand more about the properties of pharmaceutical excipients (Yu, 2008). In addition, viscosity specifications are limited when comparing CEs with different substitutions (Schmidt, Burchard, & Richtering, 2003), since it is only an average property for a polydisperse polymer, and it cannot be relied upon that polymer samples belonging to the same viscosity grade will show identical technological properties (Andersson, Wittgren, & Wahlund, 2001).

The authors believe this is the first study specifically looking at the ultrasonic degradation of pharmaceutical grade CEs with the aim of producing a range of low molecular weight polymer fractions. Ultrasonic degradation of methylhydroxyethyl cellulose (MHEC) has been performed by Pfefferkorn et al. (2003) with subsequent characterisation of the polymer undertaken using SEC-MALLS-RI apparatus (size exclusion chromatography-multi-angle laser light scattering-refractive index detection), although a non-pharmaceutical grade polymer was used in this work. Schittenhelm and Kulicke (2000) performed a similar study on a range of sulfoethyl CEs, however these derivatives are not used as pharmaceutical excipients. A detailed characterisation into the ultrasonic degradation of HPC has been reported by Malhotra (1982), using an un-identified source/grade of polymer. The emphasis of Malhotra's work was in understanding the factors (e.g. solution volume, polymer solution concentration and temperature) affecting the degradation of HPC in water, ethanol and tetrahydrofuran rather than a detailed characterisation of molecular weight. Infrared spectroscopy and X-ray analysis were performed on the degraded samples and suggested no chemical or structural changes occurred on irradiation. In the current study, a range of ubiquitous pharmaceutical grade cellulose ethers HPC, HPMC and HEC (and EHEC of non-pharmaceutical grade) were ultrasonically degraded. Both un-degraded i.e., as received from the manufacturer and ultrasonically degraded polymers were characterised with respect to molecular weight and molecular weight distribution using a range of techniques. HPC samples were additionally analysed using static light scattering in order to investigate the intrinsic viscosity–molecular weight relationship.

2. Materials and methods

2.1. Materials

Hydroxypropyl cellulose (Klucel®) and hydroxyethyl cellulose (Natrosol®) polymers were obtained from Hercules (Wilmington, USA), hydroxypropyl methylcellulose (Methocel®) from Colorcon (Dartford, UK) and ethylhydroxyethyl cellulose (Bermocoll®) from Akzo Nobel (Stenungsund, Sweden). A summary of the polymers used in the study along with the nominal molecular weight and viscosity as stated by the manufacturers is given in Table 1. The polymers were used after dissolution in water at 4 °C and lyophilisation at −57 °C using a Heto PowerDry LL3000 (Thermo Electron

Table 1
Summary of polymers including average molecular weight, method of determination and viscosity.

Polymer	Manufacturer's polymer grade	Viscosity of a 2% (w/w) polymer solution (mPa s) at 25 °C	Molecular weight (kg/mol)[a]	Molecular weight average and technique
HPC	HPC-EF	7	80	M_w (SEC)
	HPC-JF	15	140	M_w (SEC)
HPMC	HPMC E3 LV	3	8	M_n (OP)
	HPMC E4M	4000	86	M_n (OP)
HEC	HEC 250G	250–400	300	M_v ($[\eta]$)
EHEC	EHEC E230F2	300	120	NS

NS—not stated; OP—osmotic pressure; SEC—steric exclusion chromatography and $[\eta]$—intrinsic viscosity.

[a] As claimed by the manufacturer.

Co., Bath, UK) freeze dryer; the water content of the polymers determined in this way was low, typically less than 5%. Toluene (spectrophotometric grade, 99.5% purity) for static light scattering was obtained from Sigma–Aldrich (Poole, UK). Spectroscopically-pure double-distilled water was used in the preparation and dilution of polymer solutions.

2.2. Preparation of polymer solutions

Polymer solutions were prepared by weighing the required mass of polymer into a volumetric flask and adding approximately 75% of the required volume of double-distilled water whilst constantly (magnetic) stirring. Stirring was continued for a minimum of 19 h, after which the solution was made to volume with distilled water. Polymer solutions were stored in a refrigerator at 4 °C for at least 24 h prior to use to ensure complete dissolution of the polymer (Brock Neely, 1960).

2.3. Ultrasonic degradation of polymer solutions

Mechanical degradation in the form of exposure to ultrasonic radiation was performed on a range of cellulose polymers using 50 mL of a 1.5 or 4.0% (w/v) polymer solution. The polymer solution was placed in a 60 mL screw-top glass jar, and secured in a jacketed water bath with water circulating at a constant 2 °C. The temperature of the polymer solution was not routinely monitored during the sonication process. Sonication was performed using a probe sonicator fitted with a tapered microtip (Soniprobe model 7535A, Lucas Dawe Ultrasonics, UK) operating at 15% of its maximum output (150 W) with the tip of the probe positioned approximately 5 mm from the base of the jar. Polymer solutions were exposed to ultrasonic radiation for varying periods of time, typically 1, 4, 8, 16 and 24 h. The volume of polymer solution before and after exposure to ultrasonication was measured in some of the extreme experiment durations, and the difference was found to be generally less than 2 mL or less than 4% (the loss with some high molecular weight polymers was greater, but this was largely attributed to the difficulty in recovering the total amount of polymer which was of moderate viscosity). Prior to analysis of the degraded polymer samples via dynamic and static light scattering, capillary viscometry and SEC analysis, the polymer samples were first centrifuged in a Heraues Biofuge Pico ultracentrifuge (Fisher Scientific, Leicestershire, UK) for 10 min at 13,000 rpm to remove any bits of titanium shed by the probe and then lyophilised to dry the sample.

2.4. Capillary viscometry

An estimate of the viscosity average molecular weight (M_v) of the polymers was carried out by determining their intrinsic viscosity, $[\eta]$, using capillary viscometry and then applying the Mark-Houwink (M-H) equation (Eq. (1)).

$$[\eta] = KM_v^a \qquad (1)$$

where K and a are constants for a particular polymer–solvent system at a set temperature. Polymer solutions were initially diluted to ensure measurements were made below the critical concentration, C^* (defined as $1/[\eta]$). Automated measurements of the flow times of polymer solutions in a type I Ubbelohde viscometer were carried out using a Viscosity Measuring Unit AVS 350 (Schott-Geräte, Hoffheim, Germany), connected to a ViscoDoser AVS 20 piston burette (for automatic dilutions). Measurements were carried out at 20 ± 0.1 °C for HPMC and 25 ± 0.1 °C for all other polymers by immersion of the viscometer in a precision water bath (transparent thermostat CT 1650, Schott-Geräte, Hoffheim, Germany).

Table 2
Cellulose ethers and associated Mark-Houwink parameters as determined in water.

Polymer	Temp (°C)	M-H parameter[a]		Reference
		K (dL/g g/mol)$^{-a}$	a	
HPC	25	6.25×10^{-5}	0.84	Law and Kayes (1983)
HPMC	20	3.39×10^{-4}	0.88	Dow Chemicals (1975)
	20	1.86×10^{-4}	0.83	Keary (2001)
HEC	25	9.49×10^{-5}	0.87	Brown, Henley, & Ohman (1963)
MHEC		NS	NS	NS
EHEC	25	3.70×10^{-4}	0.80	Manley (1956)

NS—not stated.
[a] $[\eta] = KM_v^a$

The common intercept of separate Huggins and Kramer extrapolations to zero polymer concentration (linear regression) was used to obtain $[\eta]$ (dL/g) (Eq. (2)):

$$[\eta] = \left(\frac{\eta_{sp}}{C}\right)_{C=0} = \ln\left(\frac{\eta_{rel}}{C}\right)_{C=0} \qquad (2)$$

where η_{sp} and η_{rel} are the specific and relative viscosities respectively and C is the polymer concentration (g/dL). The use of both plots for the determination of $[\eta]$ is preferred compared to that using only one type of data evaluation (Harding, Varum, Stokke, & Smidsrod, 1991). From $[\eta]$, the M-H equation was employed to calculate M_v, with the parameters K and a for each polymer obtained from the literature (Table 2).

2.5. Steric exclusion chromatography

Steric exclusion chromatography (SEC) was performed on selected un-degraded and ultrasonically degraded polymer samples to obtain both a number-average (M_n) and weight average molecular weight (M_w) and to give an indication of the polydispersity (P_d) of the sample ($P_d = M_w/M_n$). Polymer solutions were prepared and, where appropriate, ultrasonically degraded and then lyophilised at −57 °C using a Heto PowerDry LL3000 (Thermo Electron Co., Bath, UK) freeze dryer. SEC was carried out by Rapra Technology Ltd. (Shrewsbury, UK) and was based on either an aqueous system (EHEC) or with THF (tetrahydrofuran) as the solvent/eluent (HPC and HPMC).

A solution of each polymer sample in THF was prepared by adding 10 mL of solvent to 20 mg of sample and leaving for at least 12 h to dissolve. The solutions were subsequently warmed to 50 °C for 30 min and allowed to cool, after which filtration was performed through a 0.2 μm polyamide membrane filter prior to the chromatography. SEC was carried out using a PLgel guard column plus two mixed bed-B, 30 cm, 10 μm columns (Polymer Laboratories Ltd., Shropshire, UK) with THF as the solvent, at a nominal flow rate of 1.0 mL/min at 30 °C. Detection was based on measurement of the refractive index, with differential pressure and light scattering. The data were collected and analysed using Viscotek Trisec 2000 and Trisec 3.0 software. Calibration of the polymer molecular weight was based on ten polystyrene calibrants over the molecular weight range ~3000–0.58 kg/mol (Polymer Laboratories Ltd., Shropshire, UK).

Aqueous SEC was carried out in a buffer consisting of 0.2 M $NaNO_3$ and 0.01 M NaH_2PO_4 at pH 7. Samples were prepared by adding 10 mL of this buffer to 20 mg of lyophilised polymer and leaving for at least 12 h to dissolve. Prior to injection, the polymer solutions were filtered through a 0.45 μm PVDF membrane filter. The columns used for size exclusion were two mixed –OH, 30 cm, 8 μm columns with a PLacquagel guard column. The nominal flow rate was set to 1.0 mL/min, at 30 °C with a refractive index detector. The SEC system was calibrated with ten pullulan polysaccharide calibrants over the molecular weight range ~800–0.18 kg/mol.

Table 3
Capillary viscometry, SEC and SLS data for un-degraded HPC-EF and ultrasonically degraded samples.

Duration of ultrasonication (h)	Capillary viscometry		SEC			SLS
	[η] (dL/g)	M_v (kg/mol)	M_w (kg/mol)	M_n (kg/mol)	P_d	M_w
0 (un-degraded)	1.09	112.2	110.0	40.3	2.8	138.5
1	0.95	94.9	101.0	34.5	3.0	108.0
4	0.82	79.4	ND	ND	ND	ND
8	0.69	64.5	74.5	32.2	2.3	80.0
16	0.60	55.2	ND	ND	ND	ND
24	0.53	47.0	55.4	29.5	1.9	57.5

SLS—static light scattering; ND—not determined.

2.6. Static light scattering

Selected HPC polymer solutions, prepared and ultrasonically degraded from HPC-EF and HPC-JF as detailed above, were additionally subjected to dynamic and static light scattering (DLS and SLS, respectively). Light scattering was performed using an ALV-5000 instrument with a compact goniometer system (ALV-Laser Vertriebsgesellschaft mbH, Langen, Germany). The laser source for the instrument was provided by a 22 mW He–Ne laser, operating at a wavelength of 632.8 nm. Sample cuvettes and optics were immersed in a toluene bath, which eliminated the need for corrections due to reflection at the air–glass interface since toluene has a refractive index ($n = 1.49$) close to that of glass.

The samples were diluted over a range of concentrations, typically between 0.8 and 0.2% (w/v), using water filtered several times through polycarbonate membrane filters (Micropore® GTTP, Millipore, Watford, UK) with a mean pore size of 0.2 μm. The diluted samples themselves were filtered through 0.2 μm polycarbonate membrane filters into cylindrical light scattering cuvettes (Pyrex disposable culture tubes, Corning Inc., Corning, New York, USA). Dilutions and filtrations were performed in a laminar flow cabinet to minimise dust contamination. The duration of each light scattering measurement was 10 s, averaged over a minimum of three individual runs until a statistically significant result was obtained (ALV-Correlator Software v3.0). Sample and filtered water scattering measurements were performed over the angle range 30–150° at 10° intervals. Toluene was used as the primary standard. The dissymmetry ratio, $Z_{40/140}$, i.e. the ratio of static light scattering of the polymer solution at 40° and 140° of each polymer sample, averaged over the measured concentration range, was found to be less than 1.15 indicating that the polymer molecules exhibited no significant angular dependence of scattered light intensity.

In the current study, the intensity-weighted distribution of the hydrodynamic radii (R_h) was determined from the autocorrelation function using a Laplace inversion routine, which employs the constrained regularisation method (CONTIN program) (Provencher, 1982a, 1982b). Using the R_h data obtained from the DLS measurement, the radius of gyration of the polymer, R_g, was determined by applying the theoretical relationship, $R_g = 0.205R_h$ based on the assumption that the polymer was polydisperse and exhibited a random coil architecture in water (Burchard, 2003). Since the value of R_g for all polymers was found to be less than $\lambda/20$ (31.6 nm) where λ is equal to the wavelength of the laser light source, all the polymer molecules tested were considered to act as point scatterers and thus the weight average molecular weight (M_w) of the polymer was obtained from the reciprocal of the intercept of a plot of Kc/R_θ against polymer concentration (Debye plot). K, a constant for a particular solute-solvent system was calculated using the ALV software, using a value of 0.141 mL/g for the specific refractive index increment (dn/dc) of HPC (Wittgren & Porsch, 2002). The Rayleigh ratio (R_θ) was calculated for each scattering run by the software (ALV-Correlator Software v3.0) based on the counts per second detected by the photomultiplier and corrected for scattering from the solvent and the distance between the sample and the detector. A Zimm plot was constructed for the highest molecular weight polymer tested by light scattering, i.e. HPC-JF ultrasonicated for only 1 h, to ensure that the assumption that the polymers could be considered as point sources was reasonable (Harding et al., 1991).

3. Results and discussion

The polymer solutions ranged from low viscosity for HPC-EF and HPMC E3LV to medium–high viscosity for HPMC E4M and HEC. Polymer solutions were routinely characterised with respect to molecular weight before and after exposure to ultrasonic degradation using capillary viscometry as this is a rapid and simple technique. An example of the Huggins and Kramer plots obtained for HPC-EF un-degraded (i.e., as received) and after exposure to ultrasonic radiation for varying periods of time is given in Fig. 1.

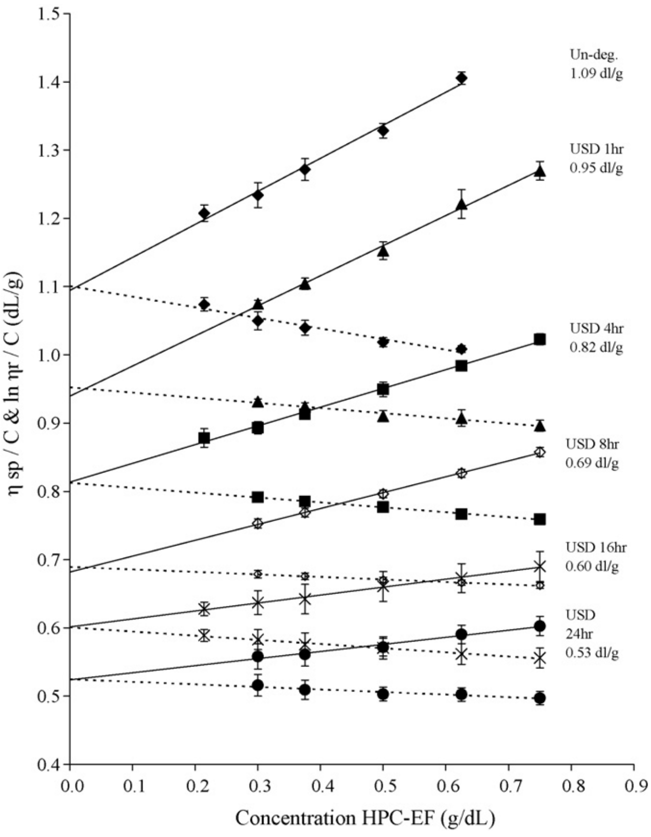

Fig. 1. Intrinsic viscosity of un-degraded and ultrasonically degraded HPC-EF samples measured at 25 °C, estimated from plots of η_{sp}/C vs. C (g/dL) (solid line) and $\ln \eta_{rel}/C$ vs. C (g/dL) (dotted line).

3.1. HPC

The [η] of HPC-EF was observed to decrease from an initial value of 1.09 to 0.53 dL/g after 24 h exposure to ultrasonic radiation. Applying the relevant Mark-Houwink equation (Table 2) to [η] determined at each degraded polymer solution gave an indication of the (viscosity average) polymer molecular weight (Table 3). Results from capillary viscometry showed the molecular weight of HPC-EF to decrease from an initial value of 112 kg/mol to a limiting (viscosity average) molecular weight of 47 kg/mol after exposure to ultrasonic degradation for 24 h under the present experimental conditions. Each molecular weight determination is from a minimum of two separately prepared and degraded polymer solutions, but from the same batch of polymer. The combined error of the ultrasonication and capillary viscometry measurements was less than 4% RSD. Increasing the concentration of HPC-EF solutions at which ultrasonic degradation was performed, from 1.5 to 4.0% (w/w) was found not to affect the resulting M_v ($p > 0.05$) (data not shown).

Also included in Table 3 are the M_w data obtained using SLS and M_n and M_w data from SEC along with an estimate of the molecular weight polydispersity. The M_w of HPC-EF from SEC and SLS was shown to correlate reasonably well with the M_v from capillary viscometry, particularly considering these determinations were obtained from three independent techniques, each involving different methods of sample preparation. Comparison of the M_w results from SEC for HPC-EF in this work with those quoted by the manufacturer (Table 1) reveals a difference of approximately 30 kg/mol, despite the manufacturer also reporting a molecular weight based on the use of SEC. This apparent discrepancy could be due to a number of factors, including the use of different calibrants for the SEC method or differences in sample preparation, combined with the fact that significant batch-to-batch variation of molecular weight has been reported for pharmaceutical grade cellulose ethers (Dahl et al., 1990). The higher M_w averages obtained from light scattering compared to those results from capillary viscometry or SEC could be a result of dust contamination or incomplete polymer hydration (Picout, Ross-Murphy, Errington, & Harding, 2001), an issue particularly relevant to the un-degraded polymer samples, but unlikely to be a factor for those exposed to ultrasonic radiation due to the high dispersing power of ultrasonic radiation.

The molecular weight polydispersity (P_d) of un-degraded HPC-EF was found to be 3.0 (Table 3) suggesting the polymer as received, exhibits a reasonable degree of polydispersity which is likely to originate from the relative high polydispersity of the source cellulose material (Doelker, 1993; Felcht, 1985). The slight increase in P_d after 1 h sonication is thought to be due to the degradation of a proportion of polymer molecules to lower molecular weights, whilst some molecules remain un-degraded. Relatively short periods of sonication may also increase the solubilisation of any large un-dissolved molecular weight fractions present before molecular weight reduction. The decrease in P_d with increasing sonication time is expected to be due to the existence of a limiting molecular weight (M_{lim}), below which little further degradation takes place. This phenomenon is well documented (Basedow & Ebert, 1977), and is due to the fact that below a certain chain length, the hydrodynamic forces arising from the application of ultrasonics are of insufficient magnitude to cause rupture of the polymer chain (Kulicke et al., 2005). The resulting P_d of the polymer of 1.9 after exposure to 24 h sonication was due to a broad but essentially monomodal molecular weight distribution as observed by DLS (Lundqvist, 1999). It is typical to see such Flory (most probable) molecular weight distribution when polymers are exposed to a random degradation process. Achieving a range of polymer molecular weight fractions with a reduced P_d could help in studies where the effect of molecular weight on product performance is being investigated since there would be less contribution from ultra-low or high molecular weight polymer chains. In fact, the application of ultrasonic radiation has been suggested as a method of reducing the polydispersity of a polymer in its own right (Marx-Figini, 1997).

Table 4
Capillary viscometry for un-degraded HPC-JF and HPC-GF and ultrasonically degraded samples.

Duration of ultrasonication (h)	HPC-JF		HPC-GF	
	[η] (dL/g)	M_v (kg/mol)	[η] (dL/g)	M_v (kg/mol)
0 (un-degraded)	1.49	163.6	4.25	566.4
1	1.25	131.7	2.31	273.8
4	1.02	103.8	1.33	142.5
8	0.84	82.2	ND	ND
24	0.59	53.9	0.65	61.1

ND—not determined.

In order to obtain a wider range of polymer molecular weights, degradation of the commercially available two next higher molecular grade polymers to HPC-EF (HPC-JF and HPC-GF) was undertaken (Table 4). Exposure of higher initial molecular weight polymers to ultrasonication led to a greater degree of molecular weight reduction. Both polymers approached a M_{lim} similar to that of HPC-EF, suggesting M_{lim} is independent of the initial molecular weight but a function of the power of the ultrasonication used. A similar trend was observed by Marx-Figini (1997) in a study of the ultrasonic degradation of cellulose and was explained by the fact that large polymer coils degrade faster due to higher interaction with the solvent in the elongational flow field. SEC of selected HPC-JF samples again revealed a good agreement with capillary viscometry data. For example, the M_w of un-degraded HPC-JF was found to be 169 kg/mol from SEC (data not shown) and 164 kg/mol using capillary viscometry (Table 4). The P_d of HPC-JF was reduced from an initial value of 4.1 to 2.2 after 24 h degradation, which approaches that found for HPC-EF (P_d = 1.9 after 24 h sonication).

3.2. HPMC

The M_n of un-degraded HPMC E4M from aqueous SEC (Table 5) was found to be lower than that stated by the manufacturer (Table 1), however the use of a different technique to determine molecular weight may explain the disparity in results, since the manufacturer states that osmotic pressure was used to determine the stated M_n. Also, the molecular weight obtained from SEC is dependent on the calibration standards used and how well they resemble the sample under analysis. Nonetheless, the intrinsic viscosity of the un-degraded polymer of 7.7 dL/g was reasonably close to that given by the manufacturer of 7.5 dL/g and to an independent determination of 7.3 dL/g as reported by Keary (2001). Despite the general agreement for measurements of [η] in the literature, there exist some differences in the Mark-Houwink exponents used and thus the values quoted for determinations of the molecular weight of HPMC. The M-H parameters quoted originally by Dow Chemicals (1975) (Table 1) have been used in a number of subsequent studies to determine the molecular weight of HPMC, for example, Law and Kayes (1983), Duro et al. (1998) and Woolenweber, Makievski, Miller, and Daniels (2000), however these parameters appear to have been constructed from M_n rather than M_w data and therefore yield a molecular weight closer to the M_n rather than M_w. The use of M_n rather than M_w to obtain M-H parameters means the 'K' value of the M-H equation is much more influenced by the P_d of the polymer samples, and caution should be exercised in using these relationships (Brandrup, Immergut, Grulk, Abe, & Bloch, 2005). The M-H parameters used for the determination of M_v in Table 5 are therefore taken from those quoted by Keary (2001) based on determinations of M_w using SEC with combined

Table 5
Capillary viscometry and SEC data for un-degraded HPMC E3 and HPMC E4M and ultrasonically degraded samples.

Polymer/grade	Duration of ultrasonication (h)	$[\eta]$ (dL/g)	M_v (kg/mol)	M_w (kg/mol)	M_n (kg/mol)	P_d
HPMC E3	0 (un-degraded)	0.61	18.7	37.4	8.4	4.5
HPMC E4M	0 (un-degraded)	7.70	382.7	119.5	35.7	3.4
HPMC E4M	1	4.25	186.5	ND	ND	ND
HPMC E4M	4	3.34	139.4	ND	ND	ND
HPMC E4M	8	2.38	92.5	ND	ND	ND
HPMC E4M	16	1.66	59.8	ND	ND	ND
HPMC E4M	24	1.16	38.8	76.2	36.7	2.1

ND—not determined.

light scattering-viscometry-refractive index detection and $[\eta]$ from capillary viscometry.

The fact that the M_w of un-degraded HPMC E4M found from SEC of 119.5 kg/mol (Table 5) was lower than that of 323–363 kg/mol found by Keary (2001) and greatly varied from previous determinations of the same polymer by our group of 687.5 kg/mol (Sepassi et al., 2007) highlighted the problem with obtaining meaningful estimates of molecular weight with the higher viscosity polymers. In particular, achieving complete dissolution of the lyophilised polymer and having to filter samples prior to SEC analysis was difficult and considered as likely sources of variation in the results. Exposure of HPMC E4M to ultrasonic radiation resulted in a reduction of the M_v after 24 h to approximately 1/10 of the initial molecular weight (Table 5). Intermediate periods of exposure between 1 and 16 h yielded a series of polymer solutions with a range of molecular weights suitable for further applications. The decrease in molecular weight was accompanied by a similar reduction in P_d after 24 h exposure as observed with HPC. It was not possible, using the current experimental set-up and ultrasonic probe, to degrade HPMC E4M to a molecular weight lower (or even of the same order) than that of HPMC E3 (18.7 kg/mol, Table 1), the lowest commercially available grade of HPMC. Even after 24 h degradation the molecular weight was approximately double that of HPMC E3 (Table 5).

Ultrasonic degradation was attempted on HPMC E3 but no decrease in M_v was found after exposure for up to 24 h (data not shown). With a M_v of 18.7 kg/mol (Table 5), the reason for the lack of sensitivity of HPMC E3 to ultrasonic radiation is thought to be due to the polymer molecular weight existing below the M_{lim} achievable using the current ultrasonic set-up and power output. It was noted that the un-degraded molecular weights obtained using capillary viscometry and SEC varied more for HPMC E3 compared to HPC-EF (Table 3) and this was attributed to the higher P_d of this polymer (Table 5).

3.3. HEC

Un-degraded HEC was found to have a $[\eta]$ of ~4.48 dL/g which gave a M_v of 236 kg/mol (Table 6) which was lower than that claimed by the manufacturer (M_v = 300 kg/mol), although the M-H parameters used for the conversion of $[\eta]$ to M_v are not stated by the manufacturer. The molecular weight determined from capillary viscometry is however close to that stated by Kiratzis, Faers, and Luckham (1999) of 223 kg/mol, but these authors do not state the method of molecular weight determination. Beheshti, Zhu, Kjoniksen, and Nyström (2007) determined a molecular weight of 400 kg/mol using light scattering although the authors do not supply experimental details. The varying results between those reported and those stated by the manufacturer as well as the lack of information regarding the methods used highlights some of the problems obtaining detailed information about pharmaceutical CEs.

Table 6
Capillary viscometry data for un-degraded HEC and ultrasonically degraded samples.

Duration of ultrasonication (h)	$[\eta]$ (dL/g)	M_v (kg/mol)
0 (un-degraded)	4.48	236.0
1	2.89	142.2
4	1.75	79.9
8	1.38	60.8
16	0.96	40.1
24	0.83	33.9

3.4. EHEC

A low molecular weight pharmaceutical grade of EHEC could not be sourced for this work, so Bermocoll E230G was used which is marketed for the paint and construction industry. As such, the manufacturer does not quote a nominal molecular weight for this polymer, relying on viscosity specifications alone. An $[\eta]$ of 4.19 dL/g found for the un-degraded polymer (Table 7) is in close agreement with the determination of the same polymer grade in water of 4.10 dL/g by Nilsson, Sundelof, and Porsch (1995). Rough agreement exists with the M_w from this work and from Nilsson et al. (1995) of 443 and 535 kg/mol respectively, the difference that does exists is likely to be explained by the different solvent used for the two SEC systems. The considerably higher values of the M_w from SEC compared to calculated M_v results from $[\eta]$ suggest that either the M-H parameters used are not accurate for this polymer, resulting in an underestimate of M_v and/or reflects the considerable degree of polydispersity that exists for this polymer (Table 7).

3.5. Comparison of cellulose ethers

A comparison of the degradation profiles (M_v vs. degradation time) for the various polymers is given in Fig. 2. The plot illustrates a characteristic exponential decrease in M_v that approaches a similar M_{lim} of 40 kg/mol for all polymers (except EHEC where

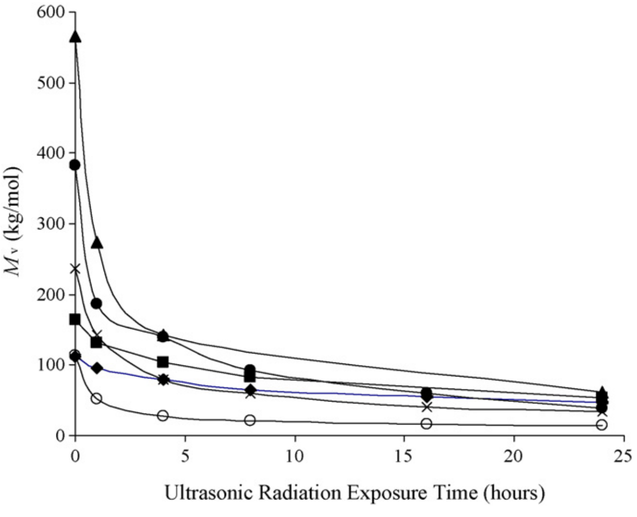

Fig. 2. Degradation plots of cellulose ether exposed to ultrasonic radiation: HPC-EF (♦), HPC-JF (■), HPC-GF (▲), HPMC E4M (●), HEC (×) and EHEC (○).

Table 7
Capillary viscometry and SEC data for un-degraded EHEC and ultrasonically degraded samples.

Duration of ultrasonication (h)	[η] (dL/g)	M_v (kg/mol)	M_w (kg/mol)	M_n (kg/mol)	P_d
0 (un-degraded)	4.19	114.0	443.0	45.2	9.8
1	2.19	52.0	ND	ND	ND
4	1.29	26.8	107.0	26.1	4.1
8	1.09	21.8	75.4	22.4	3.4
16	0.88	16.6	ND	ND	ND
24	0.79	14.5	42.6	16.6	2.6

ND—not determined.

M_{lim} = 15 kg/mol), which is independent of the initial polymer molecular weight. A similar trend was found by Schittenhelm and Kulicke (2000) in a study of the ultrasonic degradation of a range of sulfoethyl celluloses with various substituents (hydroxyethylsulfoethyl, sulfoethyl and carboxymethylsulfoethyl cellulose). The fact that a common M_{lim} was found was attributed by these authors to be due to the fact that, despite different substituents, all polymers shared the same polymer backbone and this is considered the site of chain breakage by ultrasonic radiation. The low M_{lim} obtained for EHEC of ~15 kg/mol is probably an underestimation of M_v for this polymer (as discussed above), with estimates of M_w for EHEC degraded for 24 h from SEC being closer to the M_{lim} of the other cellulose ethers (Table 7).

It is thought that the use of an ultrasonic probe with a higher power output than was used in the present study would result in more rapid molecular weight reduction. For example (Pfefferkorn et al., 2003) were able to degrade MHEC from an initial M_w of 318 kg/mol to a M_{lim} approaching 34 kg/mol after only 60 min exposure to ultrasound.

A number of different models have been proposed to describe the rate of polymer degradation upon exposure to ultrasonic radiation (Price & Smith, 1993). Wang, Ellis, & Ross-Murphy (2000) were able to model the molecular weight degradation of guar gum solutions in acidic conditions by assuming that the degradation reaction obeys first order kinetics. A similar plot of $1/M_t$ vs. t using data from the current study (Fig. 3) did not produce a linear relationship suggesting a deviation from this behaviour. Schittenhelm and Kulicke (2000) used a quasi-first order model with a term included for M_{lim} (i.e., assuming first order degradation depending on the chain length in excess of M_{lim}) originally proposed by Ovenall, Hastings, and Allen (1958) (Eq. (3)).

$$\ln\left(\frac{1}{M_{\text{lim}}}-\frac{1}{M_t}\right)=\left(\frac{1}{M_{\text{lim}}}-\frac{1}{M_i}\right)-k\left(\frac{M_{\text{lim}}}{CM_0}\right)t \tag{3}$$

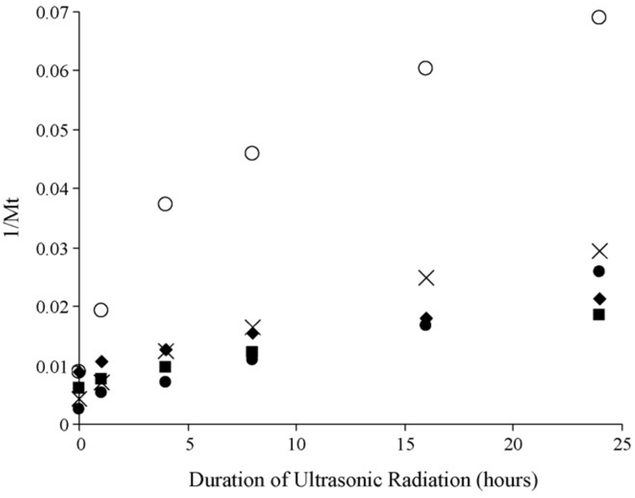

Fig. 3. First order degradation rate plot of HPC-EF (♦), HPC-JF (■), HPMC E4M (●), HEC (×) and EHEC (○).

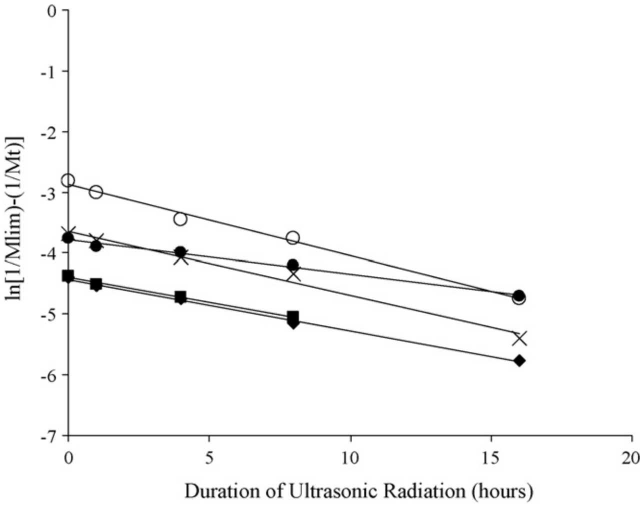

Fig. 4. Quasi-first order degradation rate plot of HPC-EF (♦), HPC-JF (■), HPMC E4M (●), HEC (×) and EHEC (○).

where M_i is the initial polymer molecular weight, M_t the molecular weight at time, t, and M_0 the monomer molecular weight. A plot of $\ln(1/M_{\text{lim}})-(1/M_t)$ vs. ultrasonic degradation time (Fig. 4) based on M_v data for the polymers degraded above (Tables 3–7) yielded average correlation coefficients of $r^2 > 0.99$ (Table 8). A good fit to Eq. (3) suggested that upon exposure to ultrasonic radiation the polymers split into two fragments of similar size (Baxter, Zivanovic, & Weiss, 2005). Similar degradation rate constants were found for the three polymers HPC, HPMC and HEC suggesting similar degradation kinetics. The higher degradation constant found for EHEC could be due to the presence of microcrystallites (Thuresson & Lindman, 1999) in the un-degraded sample, which lead to an over-estimate of the molecular weight (evidenced by the high P_d for this polymer, Table 7). Application of ultrasonic radiation then dissolves these agglomerates more rapidly than polymer chain cleavage, but has the result of an apparent rapid molecular weight degradation.

3.6. Determination of Mark-Houwink parameters for HPC

Using the [η] data obtained from capillary viscometry and the M_w from SLS, it is possible to construct a M-H plot (log[η] vs. log M_w) in order to evaluate the M-H exponents for HPC used in the present study (Fig. 5). The correlation coefficient of $r^2 = 0.99$ is

Table 8
Degradation rate constants of cellulose ethers.

Degraded polymer/grade	M_{lim} (kg/mol)	r^2	k
HPC-EF	47.0	0.996	1.048
HPC-JF	53.9	0.995	0.873
HPMC E4M	38.8	0.991	0.746
HEC	33.9	0.985	1.258
EHEC	14.5	0.992	5.461

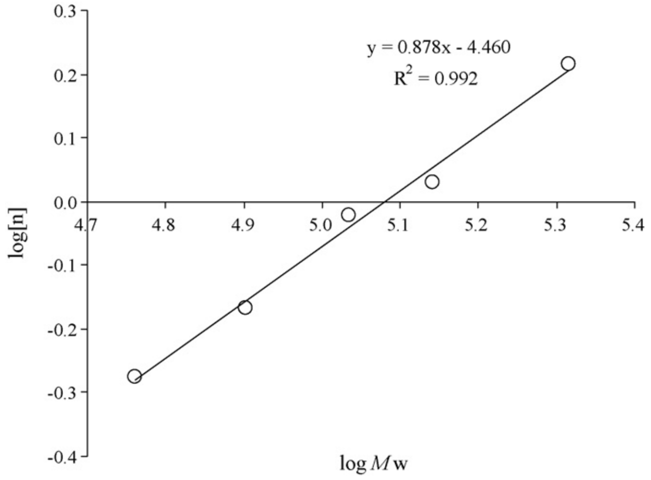

Fig. 5. Mark-Houwink plot of HPC.

considered acceptable but the relatively limited number of samples and moderate polydispersity (preferably at least four samples of different molecular weight with $P_d < 1.75$ are required) is not ideal for elucidation of M-H parameters (Brandrup et al., 2005). Reassuringly, the values of $K = 3.47 \times 10^{-5}$ and $a = 0.88$ from this work were found to be comparable to those quoted by Law and Kayes (1983) of $K = 6.25 \times 10^{-5}$ and $a = 0.84$. It is presumed however, that the M-H parameters given by Law and Kayes (1983) for HPC in water were not based on direct measurements, as the authors state that the M-H equation was established from data by Wirick and Waldman (1970) of HPC in ethanol. M_v results determined using the M-H exponents determined from Fig. 5 and the $[\eta]$ for degraded and un-degraded HPC-EF samples (Table 2) gave molecular weights approximately 17% greater than those determined using those quoted by Law and Kayes (1983). Kulicke et al. (2005) have published a list of M-H parameters for various cellulose derivatives. For HPC, they quote M-H parameters $K = 4.2 \times 10^{-4}$ and $a = 0.68$ quite different from those found for HPC in the present study however, the source, grade or molecular weight range studied are not reported.

4. Conclusion

Using ultrasonics it was possible to produce a range of polymer solutions varying in molecular weight depending on the duration (and power) of ultrasonic degradation. Samples of the lowest molecular weight grade of HPC (HPC-EF) were reduced in M_v by approximately 58%, whereas the higher molecular weight grade of HPC (HPC-JF) and other cellulose ethers were reduced by approximately 85–90%. The limiting molecular weight which was achieved by approximately 24 h was found to be independent of the type of CE or the initial polymer molecular weight. Since ultrasonic degradation does not require the addition of biological or chemical agents, the degraded polymer solutions were in a suitable form for use in further studies, for example, for studies of molecular weight on polymer adsorption or as a binder solution for wet granulation, as long as any titanium particles shed from the ultrasonic probe are removed. Determination of intrinsic viscosity from capillary viscometry measurements was found to be a rapid technique for characterising the average molecular weight of the degraded polymers. Although conversion to a M_v was complicated by the need for suitable M-H parameters for the polymer, in fact the use of $[\eta]$ in its own right has been suggested as a useful tool for characterisation of CEs (Keary, 2001) and is certainly suitable for quality control.

Acknowledgements

The authors would like to acknowledge Steve Holding at Rapra Technology Ltd. for carrying out the SEC of the polymer samples. DG would like to thank the EPSRC, Impact Faraday and GlaxoSmithKline for the award of studentships.

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