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Critical Review

Powder Compaction: Compression Properties of Cellulose Ethers

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ABSTRACT

Effective development of matrix tablets requires a comprehensive understanding of different raw material attributes and their impact on process parameters. Cellulose ethers (CE) are the most commonly used pharmaceutical excipients in the fabrication of hydrophilic matrices. The innate good compression and binding properties of CE enable matrices to be prepared using economical direct compression (DC) techniques. However, DC is sensitive to raw material attributes, thus, impacting the compaction process. This article critically reviews prior knowledge on the mechanism of powder compaction and the compression properties of cellulose ethers, giving timely insight into new developments in this field.

INTRODUCTION

Compaction can be defined as the compression and consolidation of a particulate solid–gas system as a result of an applied pressure and compression involves a reduction in bulk volume as a result of a reduced gaseous phase (Patel et al., 2006; Yihong, 2009; York, 1980). Compaction is a mechanical process in which the state of the material is changed from a powder into a compact of desired porosity. Compaction is one of the most important step in tablet production as the physical properties of the compacts, as well as the pressing forces, are determined not only by the properties of the powders constituting the powder mixture (such as particle size distribution, shape, morphology, lubrication conditions) but also by the processing conditions (Alderborn and Nyström, 1995; Ghori 2014a; Supuk et al., 2013).

Over the years, there has been considerable confusion in literature around tableting terminology. Different terms like compressibility, compactibility, and tabletability, have been used by authors to describe the same type of relationship. The root cause of this confusion is that three variables, pressure, tablet tensile strength and porosity, are not always studied simultaneously (Alderborn and Nyström, 1995; Nyström et al., 1993). Compressibility is the ability of a material to undergo a reduction in volume as a result of an applied pressure and is represented by a plot of tablet porosity against compression pressure; compactibility is the ability of a material to produce tablets with sufficient strength under the effect of densification and is represented by a plot of tablet tensile strength against tablet porosity; finally, tabletability is the capacity of a powder to be transformed into a tablet of specified strength under the effect of pressure and is represented by a plot of tablet tensile strength against compression pressure (Ghori, 2014a; Patel et al., 2006; Swarbrick, 2007).

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MECHANISM OF POWDER COMPACTION

When pressure is applied to a powder bed, the bulk volume of the powder and the amount of air are reduced; this is an endothermic process as energy is consumed during this initial volume reduction of a powder bed. Under compression, the particles are moved into closer proximity to each other and inter-particulate bonds may be established between the powder particles. The formation of bonds is associated with a reduction in the energy of the system as energy is released (exothermic process) (Coffin-Beach and Hollenbeck, 1983). In the literature, the term compression is often used to describe the process of volume reduction and the term compaction is used to describe the whole process, including the subsequent establishment of inter-particulate bonds (Adolfsson et al., 1999; Alderborn and Nyström, 1995; Sandell, 1992). The strength of a tablet composed of a certain material can be used as a measure of the compactability of that material and volume reduction takes place by various mechanisms. Different types of bonds may be established between the particles depending on the pressure applied and the properties of the powder (Adolfsson et al., 1997).

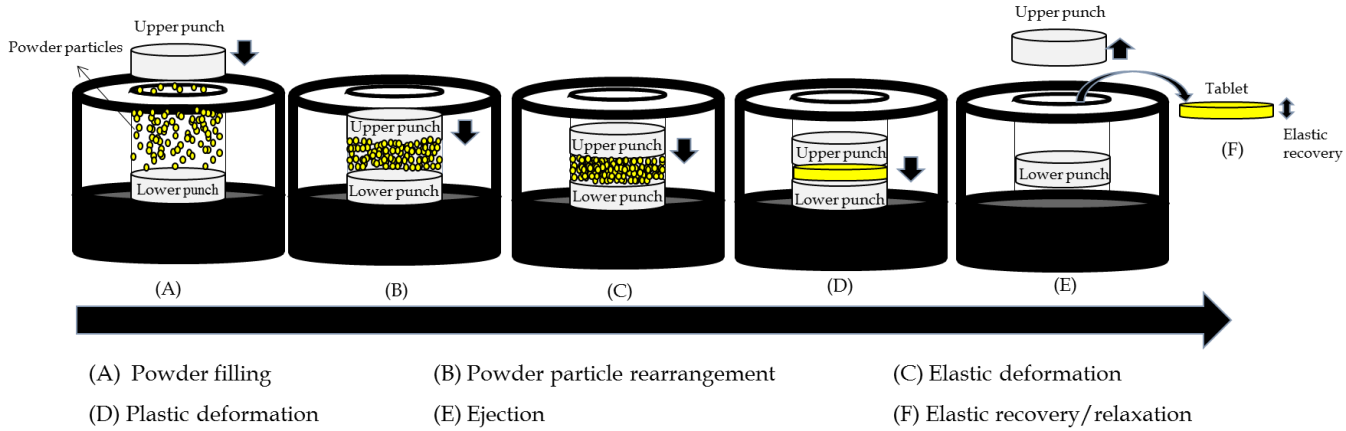

Fig.1. *Different stages of powder compaction*

The process of powder compression into a tablet (compaction) can be generally divided into four main stages, which, although sequential, in reality can occur simultaneously. These are: rearrangement of powder particles, elastic deformation of powder particles, plastic deformation and/or fragmentation of powder particles, and elastic recovery/relaxation after unloading and tablet ejection **(*Fig. 1*)**. When powder is filled into the tablet die, it is loosely packed. The powder particles are able to translocate and rotate with respect to one another to reach a state of dense packing. Soon thereafter, the system reaches a state where its capacity to rearrange itself is exhausted as the powder particles are constrained or locked into position by more structurally stable contact with their neighbours. This junction can be referred to as a constrained state, however, there is also a degree of fragmentation that can occur during this initial stage of powder compression (Alderborn and Nyström, 1995; Frenning et al., 2009). Upon reaching the constrained state, any further reduction in the porosity of the powder bed can only occur as a result of a mechanical change in the structure of each of its composing particles. Simply, there are two major routes of accommodation: deformation and fragmentation/breakage (Alderborn and Nyström, 1995; Çelik, 2011; Frenning et al., 2009; Leuenberger, 1982, Roberts et al., 1989). If the particles are elastic or plastic, they will deform to accommodate the increasing applied compression pressure. However, if a powder particle is brittle in nature, it will break into smaller pieces and, as the compression pressure increases, the surface inter-particulate voids which were formed during the initial consolidation of powder particles will be displaced. Assuming the applied compression pressure is large enough, the powder particles may go through one or all of these structural changes. It is during this transitional phase that bonding occurs between the contacting surfaces of the powder particles, either, as in the case of deformation, by an increased area of contact between particles, or by an increase in the number of bonding

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sites as in the case of breakage (Duberg and Nyström, 1981). Finally, at the maximum compression pressure, porosity is reduced to a minimum (Sonnergaard, 2000). Consequently, when the pressure is removed (unloading), the solid (tablet) begins to relax into its final dimensions, a process referred to as elastic recovery (Leuenberger, 1982). Elastic recovery/relaxation is a reversible part of deformation and higher values of elastic recovery are indicative of poor inter-particulate bonding between powder particles. The last stage in compression cycle is ejection from a die. The ejection phase also requires force to overcome adhesion between the die wall and compact surface and other forces are needed to complete ejection of a tablet (Çelik, 2011).

BONDING DURING COMPACTION

Powder particles move during the compression process and come into close proximity to each other. This provides ample opportunities for inter-particulate bonding, yet, the mechanism of consolidation by which inter-particulate bonding happens is still elusive. However, Rumpf (1958) and Turba and Rumpf (1964) proposed five possible bonding mechanisms summarised in the following sub-sections.

(a) ***Distance attraction forces;*** these involve (i) Van der Waals forces (ii) hydrogen bonding (iii) electrostatic forces (Alderborn and Nyström, 1995; Çelik, 2011; Leuenberger, 1982; Leuenberger et al., 1989; Nyström and Karehill, 1996; Patel et al., 2006; Sandell, 1992)

(b) ***Solid bridges;*** referred to the diffusion theory of bonding, they occur when two solids are mixed and form a continuous solid phase at their interface **(**Adolfsson et al., 1998; Brewin, 2007; Israelachvili, 2011)

(c) ***Non-freely movable bridges***; Powders can normally absorb water from moist air and the thickness of sorbed water layers depends on the polarity of the powder surface and the humidity of the atmosphere. In a fairly dry environment, the water will be tightly bound to a non-freely movable layer of water, which is denoted as monolayer-absorbed moisture (Ahlneck and Alderborn, 1989; Sandell, 1992; Van Campen et al., 1980; Zografi, 1988)

(d) ***Freely movable bridges***; At high relative humidity, the amount of water in the powder can increase so much that, in addition to the sorption of water, there will be a separate movable water phase, which is denoted as condensed water. Molecules of the solid can dissolve in this water which can lead to deliquescence of the solid. **(**Çelik, 2011; Crouter & Briens 2014; Lordi and Shiromani, 1984)

(e) ***Mechanical interlocking***; this is the hooking and twisting of powder particles together in a tablet (Brewin, 2007; McCormick 2005).

POWDER COMPACTION ANALYSIS

The Heckel mathematical model

The natural logarithm of the tablet porosity as a function of the applied pressure can be used to describe the compression process (Alderborn and Nystrom, 1995; Çelik, 2011). However, the Heckel equation (Eq. 1) has become the most well-known relationship describing the process relating porosity (ε) and the pressure (P) (Heckel, 1961b; Heckel, 1961a). The Heckel equation is based on the assumption that compression of powders is analogous to a first-order chemical reaction, the pores being the reactant and densification of the bulk being the product. The equation was first developed and applied to compression of metals, materials known to predominately deform plastically.

$$ln\left(\frac{1}{\varepsilon}\right) = KP + A \qquad (1)$$

A Heckel profile is normally distinguished by three different regions, an initial non-linear portion (Region I), followed by a linear part where the data obey the expression (Region II), and finally a non-linear region (Region III) (Fig. 2). The existence of these three different regions is normally explained using the underlying rate controlling compression mechanisms that dominate the respective regions. For region I, there are two main explanations proposed: firstly that the curvature is regarded to be dependent on particle rearrangement during compression (Heckel, 1961b), and secondly that the curvature is due to particle fragmentation (Israelachvili, 2011).

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Regarding the region II, it is generally accepted that particle deformation, either elastic or plastic, is controlling the mechanism of powder compression. Finally for region III, it is proposed that elastic deformation of the compact controls the process (Sun and Grant, 2001). The parameter, A, in the Heckel equation reflects low pressure densification by inter-particulate motion. The inverse of the slope (parameter K) can be calculated using the linear region. This is referred to as the Heckel parameter or the yield pressure, Py, and is commonly used as an indicator of the relative plasticity or hardness of a particle. Differences between reported values for Heckel parameters exist in the literature and may arise due to differences in determination of the linear region, deviations in the measured true densities or in the accuracy of the data acquisition. (Adolfsson et al., 1999; Adolfsson and Nyström, 1996). Finally, and most importantly, experimental conditions affect the magnitude of the Heckel parameter, such as maximum applied pressure, punch velocity or punch diameter (Kiekens et al., 2004; Patel et al., 2010).

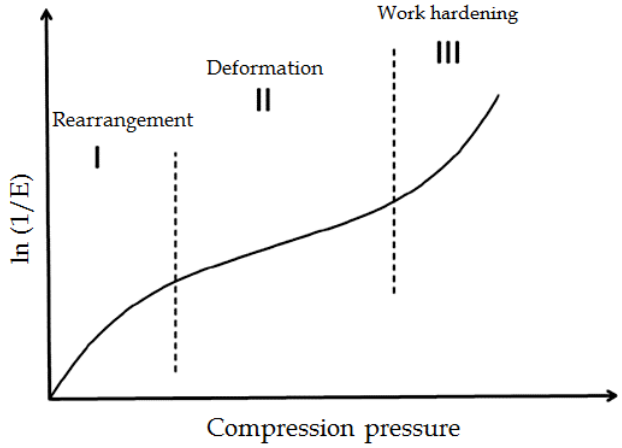

Fig. **2.** A typical Heckel plot, representing three different powder compression regions.

The Kawakita mathematical model

The basis for the Kawakita model for powder compression is that the powder particles are subjected to a compressive load in equilibrium throughout all the stages of compression, so that the product of pressure and volume is constant. The engineering strain (C) of a powder bed with respect to the applied pressure (P) is calculated using Kawakita equation (Eq. 2), which relates the strain in a powder bed to the applied compression pressure (Kawakita and Lüdde, 1971).

$$\frac{P}{C} = \frac{1}{ab} + \frac{p}{a} \qquad (2)$$

The linear relationship between P and C makes it possible to derive values for the parameters, 'a' and 'b'. The parameter 'a' represents the maximal engineering strain, C_{max}, of the powder bed, and mathematically the parameter 'b' is equal to the reciprocal of the pressure when the value, C, reaches one-half of the limiting value ($C = C_{max}/2$), as illustrated in **Fig. 3**. The Kawakita equation is often considered to be best suited for analysis of soft, fluffy powders compressed under low pressures. However, setting the start volume for the calculation is a critical point that should be carefully considered; as this has a major influence on the parameters retrieved (Kawakita and Lüdde, 1971). Physical interpretation of the Kawakita parameters has been discussed in the literature, and the inverted b-parameter (b^{-1}) is claimed to reflect the agglomerate strength (Adams et al., 1994), fracture strength of single particles or the plasticity of a granule (Nordström et al., 2008).

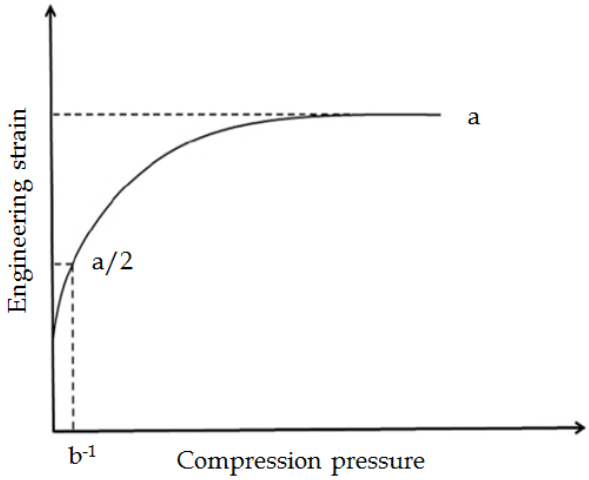

Fig. 3. A typical engineering strain (C) and compressional pressure (MPa) and interpretation of Kawakita parameters.

CHEMISTRY OF CELLULOSE ETHERS

Cellulose ethers are a commercially important class of polymer. Their physicochemical properties generally depend on their molecular weights, degree of substitution and distribution of the substitution groups. Examples of the mostly used cellulose ethers are: methylcellulose (MC), hydroxypropyl methyl-cellulose (HPMC), hydroxyethylcellulose (HEC),

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hydroxypropylcellulose (HPC) and ethyl cellulose (EC). Commonly, these polymers are used as a carrier to develop modified release matrix tablets (Alderman 1984; Asare-Addo et al., 2013; Ghori and Conway 2015; Ghori et al., 2014b; Hogan 1989; Melia, 1990; Nep et al., 2015; Timmins et al., 2014; Wen & Park 2011). However, various authors have reported their use as a binder in tablet compression because they have acceptable compaction properties (Parikh, 2016). A general chemical structure of cellulose ethers with their respective substituents (R) is shown in ***Fig. 4*** and ***Table 1***.

MC is a long chain, linear, non-ionic and substituted cellulose in which almost 27–32 % of parent hydroxyl groups are in the form of the methyl ether (Mark, 2014). ***HPMC*** is a partly O-methylated and O-(2-hydroxypropylated) cellulose, available in several grades that vary in viscosity and extent of substitution. Hypromellose contains methoxy (Meo) and hydroxypropoxy (Hpo) substituents conforming to limits for the various chemistries and molecular weight ranges from approximately 10 000–1 500 000 Da. It is a non-ionic, odourless, tasteless, white or creamy-white fibrous or granular powder. It is soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. It is available in several grades that vary in viscosity and extent of substitution (Rowe et al., 2012). Depending on the level of methoxy (Meo) and hydroxypropoxy (Hpo) substituents, there are three types of HPMC listed in the United States Pharmacopeia (USP): 2910, 2906 and 2208.

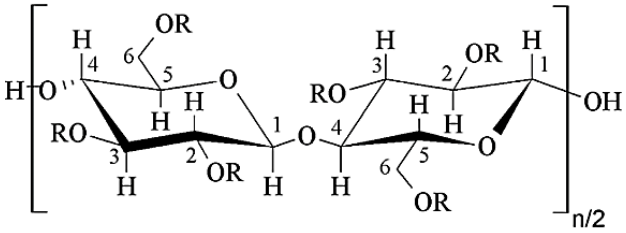

Fig.4. *Chemical structure of cellulose ethers (CE)*

The percentage limits for Meo/Hpo are 28–30/7–12%, 27–30/4.0–7.5%, and 19–24/7–12%for HPMC 2910, 2906, and 2208, respectively (Parikh, 2016). For grades originating from Ashland and Dow Chemical Company, an initial letter identifies the chemistry of the cellulose ether. "A" represents methylcellulose (MC) products "E", "F", and "K" identify different HPMC products. The number that follows the chemistry designation identifies the viscosity of that product in millipascal-seconds (mPa.s), measured at 2% concentration in water at 20°C. In designating viscosity, the letter C is frequently used to represent a multiplier of 100, and the letter M is used to represent a multiplier of 1000. Several different suffixes are also used to identify special products. For example, LV refers to special low-viscosity products, CR denotes a controlled-release grade, and LH refers to a product with low hydroxypropyl content (Dow 2006; Ashland 2012). Moreover, Shin-etsu grades can be identify using various codes; for example, MC is denoted by SM, and HPMC 2910, 2906 and 2208 are symbolised by 60SH, 65SH and 90SH, respectively (Metolose 1997).

Table 1. Cellulose ethers and substituent groups.

Cellulose ether	Substituents (R)
Methyl cellulose, MC	-H, $-CH_3$
Hydroxypropylmethyl cellulose, HPMC	-H, $-CH_3$, $-CH_2CH(OH)CH_3$
Hydroxypropyl cellulose, HPC	-H, $-CH_2CH(OH)CH_3$
Ethyl cellulose, EC	-H, $-C_2H_5$
Hydroxyethyl cellulose, HEC	-H, $-CH_2CH_2OH$

HEC is a non-ionic, partially-substituted poly hydroxyethyl) ether of cellulose. It is available in several grades that vary in viscosity and degree of substitution; some grades are modified to improve their dispersion in water. The grades are distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/v solution measured at 20 °C (Parikh, 2016).

HPC is a non-ionic partially substituted poly (hydroxypropyl) ether of cellulose. Hydroxypropyl cellulose is commercially available in a number of different grades that have various solution viscosities and molecular weight ranges from 50 000–1 250 000 (Parikh, 2016; Rowe et al., 2012).

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EC is partially ethoxylated. Ethylcellulose with complete ethoxyl substitution (DS = 3) is $C_{12}H_{23}O_6(C_{12}H_{22}O_5)_n C_{12}H_{23}O_5$ where *n* can vary to provide a wide variety of molecular weights. It is a long-chain polymer of β-anhydroglucose units joined together by acetal linkages (Rowe et al., 2012).

The high compactability of CE has been attributed to a relatively high propensity for plastic deformation and their anti-static behaviour during powder mixing (Ghori et al., 2014c; Ghori et al., 2015; Timmins et al., 2014) which enables large surfaces to be in close proximity to each other and a large number of bonds, mainly intermolecular forces, to be established between the particles (Karehill et al., 1990; Nyström et al., 1993). Mechanical interlocking may also contribute to the mechanical strength (Karehill et al., 1990).

CELLULOSE ETHERS AS A BINDER / COMPRESSION ENHANCER IN TABLET DOSAGE FORM

Nearly 80% of pharmaceutical products are administered in the form of tablets (Patel et al., 2010; Wen & Park, 2011). There are different ways of tablet manufacturing but direct compression is a straight forward, simple and fast tablet compression technique. This method is commonly used for tableting of medium to high potency drugs where the drug content is less than 30 % w/w of the formulation (Jivraj et al., 2000). One of the common difficulties in direct compression and dry granulation is poor compaction properties of drugs, especially when the amount of drug in tablet formulation is more than 30 % by weight. In these situations, an efficient compressibility enhancer can help in the production of tablets with acceptable pharmaceutical characteristics (Kleinebudde, 2004). A common feature of many such binders is that they undergo plastic deformation during compaction. However, dibasic calcium phosphate dihydrate deforms via fragmentation which is attributed to its brittle nature. Lactose is often employed in direct compression but, compared to other filler-binders, lactose exhibits relatively poor bonding properties. By modifying lactose, for example by spray drying, a material with enhanced bonding properties can be obtained (Parkih 2016; Adolfsson and Nyström, 1996). Other commonly used binders include microcrystalline cellulose, starches and their derivatives, such as pre-gelatinised and granulated starches.

Turkogula et al., (1999) used HPMC, polyethylene glycol (PEG) and Carbopol of varying concentrations (5, 10 and 20%) as a binder in a paracetamol tablet formulation. Modelling the tablet properties (hardness, friability and disintegration time) using artificial neural networks led to optimisation of a formulation containing 20% HPMC. However, Skinner et al., (1999) reported a paracetamol formulation using HPC as a binder in a roller compaction/dry granulation (RCDG) method. In this study, 4, 6 and 8% HPC was used in the formulation and it was reported that at higher HPC concentrations, tablet capping was reduced at higher compression pressure. Mitchell et al., (2003) used HPMC (low viscosity, 3 cP, 2208) in naproxen, nifedipine and carbamazepine formulations. It was concluded that the utilisation of HPMC in the slugging/roller compaction, combined with dry granulation, was an efficient process which has potential for industrial scale up. Emeje et al., (2006) concluded that EC exhibited good compaction properties when it was employed alongside with some channelling agents (sorbitol, mannitol and PEG). MC also demonstrated good compression properties when employed in metronidazole tablets (Itiola & Pilpel, 1991). Maltais et al., (2015) found the compression process produced tablets with a smooth surface when HEC was used. Hence, on these bases, it can be stated that cellulose ethers have good compaction properties and judicious use can improve compressibility of poorly compactable powder mixtures (Shokri and Adibkia, 2013).

Wet granulation processes are also employed in the development of CE-based matrix tablets. Binders are essential components of the wet granulation process. The drug substance is combined with other excipients and processed with the use of a solvent (aqueous or organic) with subsequent drying and milling to produce granules. Cellulose ethers such as MC, HPMC, HEC and HPC have good binding properties in wet granulation. Low substituted cellulose ethers, such as low substituted HPCs (L-HPC), (Desai et al., 2006) have also been used as a binder in wet granulation processes. Even though, low substituted cellulose ethers have lower water

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solubility compared with normal grades, this is offset by a very good binding efficacy (Chebli & Cartilier, 1998). Moreover, when water-soluble binders cannot be used in dosage form processing because of water sensitivity of the active ingredient, EC is often employed (Parikh, 2016). Also, CE can be used as fillers in pharmaceuticals solid dosage forms because of their compatibility with the vast majority of other pharmaceutical excipients and drugs. Furthermore, these polymers have minimal irritancy within the gastrointestinal tract (GIT) (Shokri and Adibkia, 2013).

FACTORS AFFECTING COMPACTION PROPERTIES OF CELLULOSE ETHERS

Effect of particle size

The size of CE powder particles may determine the deformation mechanism and therefore have a tendency to dictate the consolidation phenomenon (Dabbagh et al., 1996; Malamataris et al., 1994; Nokhodchi and Rubinstein, 2001; Rajabi-Siahboomi et al., 1998). Malamataris and Karidas (1994) found that when the particle size of HPMC (2208 and 2906) was reduced from <320 µm to <120 µm, the tensile strength of tablets was increased. Nokhodchi et al., (1995) investigated the effect of particle size on the compaction properties of HPMC (2208) of varying molecular sizes (100-10000 cP) and concluded that the particle size has a noticeable impact on the tensile strength of HPMC compacts, with smaller particle sizes leading to higher compact tensile strength. This is consistent with the theory that a smaller particle size allows greater packing density and a larger number of contact points between the powder particles for inter-particulate bonding (McCormick 2005). The compressibility index (CI, %) is frequently used to assess the powder compressibility and it gives information regarding the flowability of powders with the CI of HPMC decreasing with increasing particle size (Çelik 2011). However, the yield pressure (Py) values of different HPMC grades were reported to be independent of particle size. Additionally, it was reported by Nokhodchi et al. (1995) that elastic recovery increased as the particle size increased, indicating greater inter-particulate bonding between the fine powder particles. Fine particle size grades of HPC have also shown favourable compression properties in direct compression, however, the regular particle size grades possess more water dispersible characteristics making them useful for binders in wet granulation processes in tablet manufacturing (Picker-Freyer 2007). Selmeczi, 1975 and Alvarez-Lorenzo et al., (2000) highlighted the compression enhancing performance of HPC in which tablets had a short disintegration time but high mechanical strength. Similarly, the fine particle size grades of MC, EC and HEC have good compression properties and thus can be utilised as binders in direct tablet compression process (Desai, 2001; Mark, 2014; Parikh, 2016).

Effect of chemical substitution

The levels of Hpo and Meo substitution of HPMC grades (%) (i.e. F4M, E4M and K4M) have a marked effect on the compaction properties of matrices (Rajabi-Siahboomi et al., 1998; Nokhodchi and Rubinstein, 2001). K4M exhibited greater packing ability than F4M and E4M, however, F4M produced compacts with higher strength than K4M at the same compression pressure. Moreover, it was also reported that the increase in Meo/Hpo substitution ratios leads to an increase in Py (Malamataris and Karidas, 1994; Malamataris et al., 1994). It is further reported by Rajabi-Siahboomi and Nokhodchi (1999) that A4M (MC) has the ability to produce tablets with higher tensile strength in comparison to F4M, E4M and K4M. Gustafsson et al., (1999) studied the effects of substitution on the particle characteristics and compaction behaviour of HPMC obtained from two different suppliers. Low, medium and high substitution ratios were studied using Methocel® K4M, E4M and F4M and compared with Metolose® 90 SH 4000, 60 SH 4000 and 65 SH 4000, respectively. Differences in drug release from Methocel® E4M matrices compared with the other two Methocel® products were related to a reduced powder surface area, differing particle morphology and lower fragmentation propensity (Gustafsson et al., 1999). Additionally, E4M compacts were weaker and had different porosity and elastic recovery. There were no differences between the polymers in the degree of disorder, as evaluated by solid-state NMR spectroscopy (Gustafsson et al., 1999). After a series of studies, Escudero et al., (2008, 2010 and 2012) concluded that A4M (MC) has best compaction properties, which might be due to the absence of hydrophilic Hpo groups. It was reported that the

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A4M has a plasticity index (PI) of 99.0 %, which is higher than F4M (96.8 %), E4M (95.2 %) and K4M (97.0 %). Moreover, it was also reported that the substitution levels influenced pores on the surface of tablets as the K4M compacts have macroscopic pores (601 Å) whereas A4M, F4M and E4M have microscopic surface pores (Escudero et al., 2008; Escudero et al., 2012). On the basis of these findings, it can the hypothesised that the surface pores might be related to Hpo/Meo ratio as the K-chemistry polymers have a higher ratio than E, F and A chemistry HPMCs. A study conducted by Desai et al., (2006) concluded that the low substituted HPCs have good binding properties in direct and wet tablet granulation processes. However, a higher degree of substitution render HPC more thermoplastic (Parikh, 2016) Moreover, other chemically distinct CE grades (EC and HEC) have also showed acceptable/good compression properties (Desai, 2001; Mark, 2014).

A summary of various factors affecting compression properties of CE is given in Table 2.

Table 2. Summary of various factors affecting compression properties of cellulose ethers

Factors	Effect	References
Particle size	A reduction in particle size leads to higher tensile strength of matrix tablets	Alvarez-Lorenzo et al., 2000; Desai et al., 2001; Malamataris and Karidas, 1994, Malamataris et al., 1994, Nokhodchi et al., 1995, Rajabi-Siahboomi et al., 1998, Nokhodchi and Rubinstein, 2001; Picker-Freyer 2007; Selmeczi, 1975
Substitution	Tensile strength of tablets increases with increased presence of the hydrophobic group (Meo). However, the P_y values decrease	Desai et al., 2001; Escudero et al., 2008; Escudero et al., 2010; Escudero et al., 2012; Malamataris and Karidas, 1994, Malamataris et al., 1994; Mark, 2014; Nokhodchi and Rubinstein, 2001; Rajabi-Siahboomi et al., 1998, Rajabi-Siahboomi and Nokhodchi, 1999, Parikh, 2016
Viscosity (Molecular size)	Higher viscosity grades have a tendency to produce low tensile strength tablets and have higher P_y values.	Escudero et al., 2008; Malamataris et al., 1994; Nokhodchi et al., 1996b; Nokhodchi and Rubinstein, 2001
Humidity	Higher moisture content leads to increased tensile strength of tablets.	Malamataris and Karidas, 1994; Nokhodchi et al., 1996a; Nokhodchi et al., 1996c; Rajabi-Siahboomi et al., 1998; Nokhodchi and Rubinstein, 2001; Parikh 2016

Effect of molecular size

The compression and compaction properties of CE are affected by viscosity grade (Nokhodchi and Rubinstein 2001; Parikh, 2016). It was reported by Nokhodchi et al. (1996a) that as the viscosity of HPMC decreases, the ability of powder particles to deform plastically increases and the tensile strength of HPMC K100 is much higher than other HPMC grades as a consequence of its viscosity. The increase in molecular weight might affects the material's ability to deform. This might be due to low viscosity HPMC having shorter polymeric chains and these can deform readily to fill inter-particulate gaps (Nokhodchi et al., 1995). However, Malamataris et al., (1994) found that the Py of HPMC tablets was not affected by polymer viscosity grade. The average surface pore size of K100M based compacts was 434.5 Å and considered to be microscopic, compared to a pore size in K4M compacts (601.0 Å) of macroscopic dimensions but the molecular size had no effect of the PI (Escudero et al., 2008). However, molecular weight plays a vital role in determining the compression ability of HPC and it was observed that the low molecular weight grades are most typically used as binders (Parikh, 2016).

Effect of humidity

Increased moisture uptake causes a decrease in tensile strength of tablets due to weak inter-particulate bonding caused by softening of the HPMC (Malamataris and Karidas 1994). The thickness of K4M (HPMC) compacts fell as the moisture content increased from 0 to 14.9% w/w (Nokhodchi et al., 1996b), which also resulted in a marked increase in the tensile strength of the tablets. The increase in moisture content also reduced the elastic recovery of the compacts because of greater tablet consolidation. The influence of moisture content on Heckel analysis, energy analysis and strain-rate sensitivity of HPMC 2208 has also been reported. An increase in moisture content from 0 to 14.9 % w/w decreased the mean Py, probably because of a plasticising effect of moisture that reduced the resistance of particles to deformation

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(Nokhodchi et al., 1996c). The strain-rate sensitivity, which is the ability of the material to resist necking, increased from 21.6 to 50.7 % as the moisture content increased from 0 to 14.9% w/w, indicating that the plasticity of HPMC increased with an increase in moisture content (Nokhodchi et al., 1996c).

CONCLUSIONS

In conclusion, it is evident from the studies that the cellulose ethers have good compression and consolidation properties. However, the mechanism of deformation is markedly affected by their inherent properties (particle size, chemistry and molecular size/viscosity). Moreover, the impact of humidity, batch to batch variation and different manufacturing processes on the compression properties is also reported. It can also be concluded that all the cellulose ether powders, especially MC and HPMC deform plastically. Additionally, the information extracted from the current review article can be used in the development and further optimisation of compressed hydrophilic matrices.

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