European Journal of Pharmaceutical Sciences 65 (2014) 1–8

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

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

Tribo-electric charging and adhesion of cellulose ethers and their mixtures with flurbiprofen

Muhammad U. Ghori, Enes Šupuk, Barbara R. Conway *

Department of Pharmacy, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, United Kingdom

ARTICLE INFO

Article history:
Received 13 March 2014
Received in revised form 25 July 2014
Accepted 24 August 2014
Available online 1 September 2014

Keywords:
Tribo-electrification
Surface adhesion
Electrostatic charging
Hydroxypropyl methylcellulose
Methylcellulose
Flurbiprofen

ABSTRACT

The pervasiveness of tribo-electric charge during pharmaceutical processing can lead to the exacerbation of a range of problems including segregation, content heterogeneity and particle surface adhesion. The excipients, hydroxypropyl methylcellulose (HPMC) and methylcellulose (MC), are often used in drug delivery systems and so it is important to understand the impact of associated factors on their charging and adhesion mechanisms, however, little work has been reported in this area. Such phenomena become more prominent when excipients are introduced to a powder mixture alongside the active pharmaceutical ingredient(s) (APIs) with inter- and intra-particulate interactions giving rise to electrification and surface adhesion of powder particles. The aim of this study was to understand the impact of material attributes (particle size, hydroxypropyl (Hpo) to methoxyl (Meo) ratio and molecular size) on the charging and adhesion characteristics of cellulose ethers. Furthermore, a poorly compactible and highly electrostatically charged drug, flurbiprofen, was used to develop binary powder mixtures having different polymer to drug ratios and the relationship between tribo-electric charging and surface adhesion was studied. Charge was induced on powder particles and measured using a custom built device based on a shaking concept, consisting of a Faraday cup connected to an electrometer. The diversity in physico-chemical properties has shown a significant impact on the tribo-electric charging and adhesion behaviour of MC and HPMC. Moreover, the adhesion and electrostatic charge of the API was significantly reduced when MC and HPMC were incorporated and tribo-electric charging showed a linear relationship (R^2 = 0.81–0.98) with particle surface adhesion, however, other factors were also involved. It is anticipated that such a reduction in charge and particle surface adhesion would improve flow and compaction properties during processing.

1. Introduction

Tribo-electrification is intrinsically a dynamic, strenuous and dissipative phenomenon, which is generated due to the difference in electrical potential when two materials come into contact with each other (either by impact, friction or shear) and then separated (Harper, 1967). The charge duration on a surface depends on relaxation time, which is the product of permittivity and surface resistivity of materials. As the majority of pharmaceutical materials are insulators, this process is extended, perhaps over minutes to hours, in comparison to conductive materials (Bailey, 1984; Rowley, 2001). A fundamental understanding of the phenomenon is still elusive (Soh et al., 2012), however, on the basis of existing theories, the mechanism of charge generation can be due to electron transfer, (charge is produced due to the flow of electrons between particles); ion transfer (diffusion of ions between the surface of particles); or due to material transfer (some material is rubbed off from one contacting body and attached onto the surface of another particle). Commonly, the tribo-electric charging process is a combination of these processes, although the charging behaviour of pharmaceutical materials is usually ascribed to the electron transfer theory because it provides a relatively understandable description of the charging process (Matsusaka et al., 2010). During the contact charging process, the valence electron energy state of powder particles on an atomic scale is designated as the fermi level whilst the vacuum energy level is a thermodynamic state of electrons far from the atom and can be considered as a reference point. The difference between the fermi level and vacuum energy level equates to the work function (Φ), which is a unique surface property of materials and refers to the minimum energy difference required for the liberation of loosely bonded electrons present in the outer electron shells of an atom (Lowell, 1979). When inter or intra-particulate contacts of powder particles are established,

* Corresponding author. Tel.: +44 (0)1484 472347; fax: +44 (0)1484 472182.
E-mail address: b.r.conway@hud.ac.uk (B.R. Conway).

http://dx.doi.org/10.1016/j.ejps.2014.08.010
0928-0987/

electrons flow from the lower work function (Φ_1) towards the higher (Φ_2), consequently a potential difference (Φ_2–Φ_1) is generated across the particle surface (Lang and Kohn, 1971). Moreover, this leads to the generation of electrostatic charge, which is exclusively a surface phenomenon (Lowell and Rose-Innes, 1980).

During pharmaceutical powder processing (e.g. milling, transporting, mixing, coating, spray drying, pneumatic conveying and sieving) particles develop tribo-electric charge due to the frequent abrasion and collision between the powder particles and the contacting surface of the processing equipment (Cross, 1987; Cross et al., 1981; Lowell and Rose-Innes, 1980). This can instigate problems such as dust explosions, particle adhesion during manufacturing, alteration in the dose uniformity of dosage form, particle accumulation on the surface and segregation (Hussain et al., 2013; Pu et al., 2009; Staniforth and Rees, 1981, 1982; Šupuk et al., 2011). The chemical structure, functional groups, surface chemistry (Kamiyama et al., 1994; Mazumder et al., 2006; Shinohara et al., 1976), particle size, shape, surface roughness (Carter et al., 1998; Eilbeck et al., 1999; Traini et al., 2012) and electrical properties of powders and contacting surfaces (Bailey and Smedley, 1991; Rowley, 2001) can all affect the tribo-electrification process and subsequent particle surface adhesion. Moreover, the charge transfer process is further complicated due to external factors that may influence the charging process including relative humidity, temperature, nature of contacting material and the velocity of particles (Matsusaka et al., 2010). Despite the negative influences described above, electrostatic charging phenomena can be beneficial under certain conditions, for example, exploiting the opposite polarity of charged powder particles to fabricate ordered mixtures (Mäki et al., 2007). Electrostatic assisted ordered mixtures are considered stable and further have a potential to improve content homogeneity, stability and powder processing problems (Karner and Urbanetz, 2011; Mäki et al., 2007; Staniforth and Rees, 1981).

Numerous varieties of pharmaceutical excipients are employed to improve or modulate tablet characteristics, among them methylcellulose (MC) and hypromellose (HPMC) are frequently used for controlling drug release from hydrophilic matrix systems (Ghori et al., 2014; Li et al., 2005; Maderuelo et al., 2011). These polymers are available in different grades varying in viscosity (molecular size), substitution ratios and particle size.

Asare-Addo et al. (2013) recently described the tribo-electric charging behaviour of Methocel® E4M, K4M and their powder mixtures with the negatively charging API, theophylline. The polarity of the polymers alone was positively charged, unlike the majority of other excipients previously reported, and was generally higher in magnitude than other common pharmaceutical excipients (Šupuk et al., 2012). It was shown that when theophylline came into contact with HPMC, it attached to its surface due to opposite polarities and the tribo-electric charge of the final powder mixture was decreased (Asare-Addo et al., 2013). Surprisingly, despite being so widely used, the tribo-electrification and adhesion characteristics of MC and HPMC and their subsequent impact on API in a binary system is still poorly understood. Flurbiprofen was used as a model drug and has been known for its poor mechanical, electrostatic and adhesion properties (Chow et al., 2012; Šupuk et al., 2013, 2012; Wang et al., 2004). The aim of this study was to investigate the tribo-electrification and adhesion properties of different cellulose ethers and flurbiprofen. The impact of polymer attributes (concentration, particle size, hydroxypropyl (Hpo)/methoxyl (Meo) substitution ratio and molecular size) on tribo-electric charging and surface adhesion of cellulose ethers and their powder mixtures with API were studied. Furthermore, a relationship between tribo-electric charging and surface adhesion was also studied.

2. Materials and methods

2.1. Materials

Flurbiprofen was purchased from Aesica Pharmaceutical Ltd. (Cramlington, UK). Methylcellulose, (Methocel® A4M) and hydroxypropyl methylcellulose (Methocel® F4M, E4M, K4M, K15M and K100M) were donated by Colorcon Ltd. (Dartford, UK) and specifications are listed in Table 1. In particular, K grades (hypromellose 2208) have a methoxy substitution of 19–24% and a hydroxypropyl substitution of 7–12%. F grades (hypromellose 2906) have a methoxy substitution of 27–30% and a hydroxypropyl substitution of 4.0–7.5%. E grades (hypromellose 2910) have a methoxy substitution of 28–30% and a hydroxypropyl substitution of 7–12%. A grades (Methyl cellulose) have only methoxy substitution of 27–32% (Table 1). The first letter is followed by an indication of the viscosity of their aqueous 2% w/w gels (centipoise) at 20 °C, with a multiplier of 100 (denoted by the letter C) or 1000 (denoted by the letter M).

2.2. Methods

2.2.1. Powder preparation and characterisation

Particle size fractions of each polymer (90–150 μm and 150–250 μm) and flurbiprofen (38–63 μm) were obtained through mechanical sieving. Moreover, all the powders were stored at ambient temperature (18–24 °C) and humidity (RH 36–44%) before any further investigations. Surface morphology was imaged using scanning electron microscopy (SEM). All samples were sputter-coated with gold/palladium (80:20) for 60 s using the Quorum SC7620 Sputter Coater and samples imaged using the Jeol JSM-6060CV SEM under vacuum.

2.2.2. Preparation and storage of powder mixtures

Binary powder blends of flurbiprofen (38–63 μm) and the cellulose ethers (90–150 μm and 150–250 μm size fractions) were prepared as described in Table 1, at a fixed polymer to drug ratio of 0.5%, 1%, 2.5%, 5%, 10% and 15% w/w. The powder samples were tumble mixed for 20 min (50 rpm) and stored at an ambient temperature (18–24 °C) and humidity (RH 36–44%).

Table 1
Specifications of methylcellulose (MC) and hypromellose (HPMC).

Polymer grade	Methoxy (Meo) (% w/w)[a]	Hydroxypropyl (HPO) (% w/w)[a]	Hpo/Meo ratio	Total degree of substitution (% w/w)	Viscosity (cps)[a]	Average molecular weight (g/mol)[a]
Methocel® A4M	30	0	0	30	4878	~86,000
Methocel® F4M	28.1	6.7	0.238	34.8	4031	~90,000
Methocel® E4M	29.0	8.3	0.286	37.3	3919	~92,000
Methocel® K4M	22.3	8.5	0.381	30.8	4351	~88,000
Methocel® K15M	22.3	9.0	0.403	31.3	17,129	~125,000
Methocel® K100M	22.5	8.9	0.395	31.4	79,279	~215,000

[a] Data obtained from the manufacturer (Dow, 2002).