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Tribo-electric Charging and Adhesion of Cellulose Ethers and their Mixtures with Flurbiprofen.

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Graphical abstract

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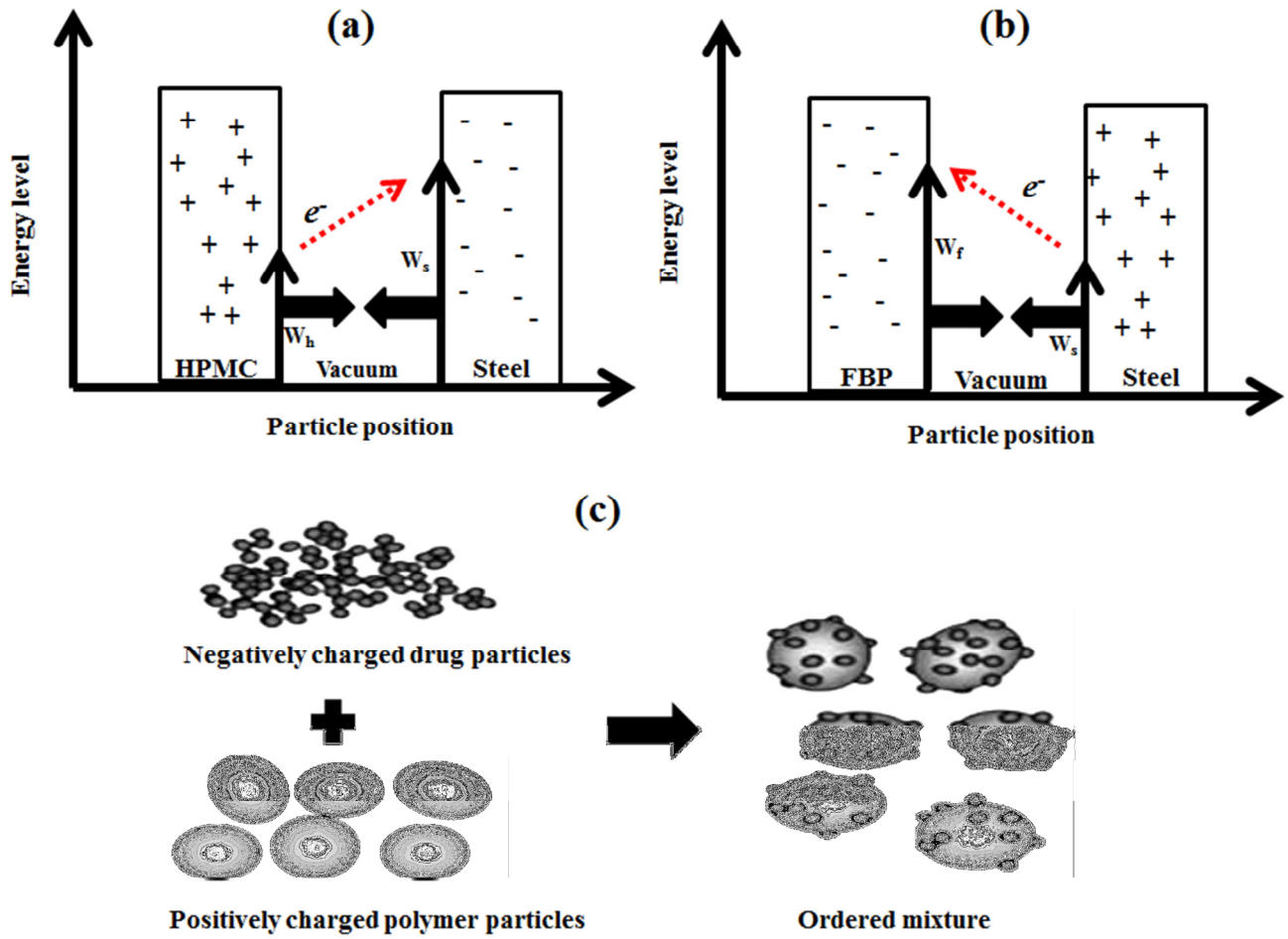

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Abstract

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, hydroxypropoxyl (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 physicochemical 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.

Keywords:

Tribo-electrification, Surface adhesion, Electrostatic charging, Hydroxypropyl methylcellulose, Methylcellulose, Flurbiprofen.

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, electrons flow from the lower work function (Φ_1) towards the higher (Φ_2), consequently a potential difference ($\Phi_2 - \Phi_1$) 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 Anne 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; Šupuk *et al*., 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 seconds 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 minutes (50 rpm) and stored at an ambient temperature (18-24 $^{\circ}$C) and humidity (RH 36-44 %).

2.2.3- Efficiency of mixing

To ensure a homogeneous powder mixture, random samples of 10 mg were taken from each batch (n=3), dissolved in phosphate buffer pH 7.2 (100 ml), and filtered using a 0.45 µm PTFE syringe filter. Flurbiprofen concentration was determined by using UV-Vis Spectrophotometry (Jenway 6305, UV-VIS spectrophotometer, λ_{max} = 247 nm) and an acceptance limit of 95 – 105% was set (BP, 2012).

2.2.4-Tribo-electrification

Tribo-electric charge to mass ratio (*Q*/*M*) was determined using an electrostatic charge measurement apparatus, based on a shaking concept (Šupuk *et al.*, 2009). Powder (~ 0.1 g) was placed inside a stainless steel cylindrical container (10 ml) and shaken in a horizontal direction (Retsch MW 4000) for 0.5, 2, 5 and 10 minutes at a vibration frequency of 20 Hz. The charged powder particles were then poured into a Faraday cup, connected to an electrometer (Keithley Model 6514). A Faraday cup comprises two concentric cups made up of a conducting material. The outer cup is slightly larger and acts as an electrical shield and it is covered by a lid. Both are very important to prevent the effect of any extraneous electric fields. The inner cup is directly attached to an electrometer for charge measurement and can be removed to measure the weight of the sample poured. The two cups are separated by a PTFE insulator. As charged samples are loaded into the inner Faraday cup, this induces an equal but opposite charge on the wall of inner faraday cup, providing the net charge on the object

(Asare-Addo *et al*., 2013; Šupuk *et al*., 2013). The resolution of the charge measurement was in nano-coulombs (nC). The charge to mass ratio (*Q/M*) was calculated by dividing the final charge with the final mass of the respective powder.

Each tribo-electric charging test was repeated three times and the shaking container was cleaned between each test by washing with isopropyl alcohol to remove any residual deposits, impurities and surface charges. Studies were carried out at an ambient temperature (18-24 $^{\circ}$C) and humidity (RH 36-44 %). Maximum charge was gained after shaking for 0.5 minutes for polymers and 5 minutes for flurbiprofen and powder blends of polymer/flurbiprofen. Maximum charge acquisition data are presented as charge to mass ratio (*Q/M*) at the end of each tribo-electrification experiment (n= 3).

2.2.5- Surface adhesion

During powder processing powder particles can adhere to equipment surfaces, resulting in loss through deposition and this may cause a change in proportionalities within powder mixtures. It is important to determine the propensity for particle adhesion for drugs, excipients and their mixtures. Following each tribo-electric charging test the powder was recovered from the Faraday cup. It is important that any adhered powder is not removed by scraping as this may affect charging so the loose powder was removed by gentle tapping on the outside of the container several times thereby dislodging the charged powder into an empty Faraday cup. Particle adherence to the surface of the stainless steel container used in the tribo-electrification studies was calculated from mass difference by deducting the final amount recovered (post-shaking and tapping) from the initial amount of sample loaded into the shaking vessel (Šupuk *et al*., 2012) and powder mass loss was demonstrated as a percentage (%) of powder adhesion.

2.2.6- Statistical analysis

Analysis of variance (ANOVA) (confidence limit of $P < 0.05$) was used to investigate the statistical significance of different underlying factors on tribo-electrification and adhesion properties of polymers and their blends with flurbiprofen.

3-Results and discussion

3.1- Characterisation of powders

3.1.1- Morphology of cellulose ether powders

All the grades of HPMC and MC contained mixtures of irregular-shaped flat and fibrous particles (Figure 1a and b and supplementary data Figure 1a - d). Generally, the proportion of fibrous material is higher in MC than HPMC. The K-chemistry grades of HPMC and, in particular, K100M contain more irregularly shaped particles with rough surfaces than any of the other grades of cellulose ethers. This is attributed to the higher Hpo/Meo substitution ratio and molecular size which result in more complex surfaces (Gustafsson *et al*., 1999; Okimoto *et al.,* 1997).

3.1.2- Tribo-electrification and adhesion behaviour of polymers

All grades of cellulose ethers charged positively against the stainless steel container (Table 2). The charge and surface adhesion ranged between 4 - 57 nC/g and 6 - 33 %. The order of charging and particle surface adhesion was A4M > F4M > E4M > K4M >K15M > K100M with the amount of charge transferred assumed to be due to differences in the effective work function between the contacting surfaces. The cellulose ethers have a lower effective work

function than the steel surface, therefore it is assumed that electrons from the surface of polymer particle move to the interface of the contacting surface inducing a positive surface charge on the donor, with a negative charge (acceptor) on the steel surface (Figure 2a). An equilibrium state is reached when both the potential difference and charged layers become equal in magnitude. As the particle moves away from a contact point, the initial high magnitude of capacitance is reduced (Matsusaka *et al.*, 2010). The potential difference between the materials initiates cohesive and adhesive interactions, with the latter apparently having a dominant role in particle adherence to the contacting surface (Cross, 1987). The propensity and magnitude of inter-particulate forces within pharmaceutical powders often seem to be directly related to the powder particle size (Rowley, 2001). In this study, the charge and adhesion of A4M was increased by 3.1 nC/g and 3.3 % respectively when particle size was reduced from 150 – 250 to 90 - 150 µm. This trend is exhibited by all HPMC grades except the very low charging K100M (Table 2). The tribo-electric charge and adhesion of polymer are inversely related to particle size ($P < 0.05$, Table 2); presumably, fine particle fractions have a large specific surface area thereby increasing the number of particle and surface contacts (Cross, 1987; Rowley, 2001). Moreover, particle size can also influence the effective work function of the materials as larger particles might lose their electrons easily, decreasing the effective work function(Gallo and Lama, 1976).

When two dissimilar materials such as metals and polymers contact, the magnitude and polarity of tribo-electric charging, is determined by functional groups, structural and surface chemistries (Kamiyama *et al*., 1994; Mazumder *et al*., 2006; Sharma, 2004; Shinohara *et al*., 1976; Trigwell *et al*., 2003). It can be hypothesised that the substitution ratio on the anhydrous glucose ring of cellulose ethers and their molecular size will alter the charging and adhesion behaviour due to variations in electrical resistivity and effective work function and this was

borne out in this study ($P<0.05$). These materials are manufactured commercially from the parent cellulose which is highly crystalline and insoluble in water. However, various substitution groups (methyl chloride and/or propylene oxide) can be integrated along the anhydrous glucose backbone which helps to reduce crystallinity and impart solubility (Sarkar and Walker, 1995). Previous studies have reported that degree of crystallinity and modifications to surface composition can alter the effective work function of pharmaceutical powders (Kamiyama *et al*., 1994; Mazumder *et al*., 2006; Murtomaa *et al*., 2002; Wong *et al*., 2014). As the ratio of the hydrophilic substitution group, hydroxypropoxyl, increased (with respect to methoxy groups), the charge and surface adhesion decreased (Table 2). Therefore, methylcellulose, A4M (i.e. 0 % hydroxypropoxyl substitution) has the highest tribo-electric charge and surface adhesion. K4M, which has a higher Hpo/Meo substitution ratio (0.382), but similar molecular weight as Methocel F4M and E4M, shows lower propensity of charge and surface adhesion (Table 2). So, the tribo-electric charging and surface adhesion behaviour of HPMC and MC can be assumed to be related to work function variations induced during the substitution process.

Cellulose ethers are polydisperse molecules with longer chain lengths increasing viscosity (Sarkar and Walker, 1995). Polymeric chains in K100M are longer than those in K15M and K4M and generate the lowest tribo-electric charge and surface adhesion. The magnitude of charge and surface adhesion decreased with increasing polymer chain length within the HMPC series (i.e. K4M >K15M >K100M (Table 2). The arrangement and length of the polymeric chains affect the surface roughness, physical, rheological and mechanical properties of the particles (Keary, 2001). Therefore, it can be anticipated that the molecular size and arrangement of polymeric chains within HPMC particles modifies the polymeric architecture and localises change in the atomic structure, resulting in alteration of electrical resistivity and

effective work function. These characteristics dictate the charge transfer process and generation of operational forces (van der Waal forces, ionic bonding and electrostatic forces) thus impacting surface adhesion phenomena (Harper, 1967).

3.1.3- Charging and surface adhesion of flurbiprofen

Flurbiprofen, like many other active pharmaceutical ingredients, possesses a high degree of crystallinity (Oh *et al*., 2011; York, 1983) and was presumed to have a higher effective work function than the contacting surface (stainless steel) due to its greater electrical resistivity. Therefore electrons from the stainless steel surface would move to the interface of the contacting flurbiprofen powder particles, inducing a positive surface charge on the donor, with a negative charge (acceptor) on the flurbiprofen particles (as illustrated in Figure 2b). Flurbiprofen had a negative net charge across its surface (-243 nC/g) resulting in a higher magnitude of surface adhesion (74 %) due to the dispersive, chemical and electrostatic forces. This electrostatic behaviour can be categorised as highly charging when compared to other APIs and pharmaceutical excipients (Šupuk *et al*., 2012) and is likely to result in processing problems during tabletting.

3.1.3- Efficiency of mixing process

Differential scanning calorimetry and powder X-ray diffraction did not highlight any concerns with respect to interactions (results not shown). Among different mixing methods, ordered mixing results in a more homogeneous and stable particulate system. Ordered mixing can be achieved by using powder particles having electrostatic charges of opposite polarity (Mäki *et al*., 2007; Swaminathan and Kildsig, 2000; Venables and Wells, 2001). Drugs are usually negatively charged while the excipients or polymers are positively charged. This can

been used to maintain the homogeneity of a mix through processing conditions (Saharan *et al*., 2008). In the present study an ordered binary mix was formed by mixing a polymer (positively charged) and flurbiprofen (negatively charged) powders (Figure 2c). All binary mixtures were analysed and contained between 95 - 105% of the expected flurbiprofen content. Charge generation due to tribo-electrification phenomena is considered to be the main contributing factor to the stability of these binary mixtures. It was observed that the negatively charged flurbiprofen particles were attracted towards the positively charged polymeric powder particles and adhered to their surfaces (Figure 1 c and d, Figure 2 c and supplementary data Figure 1 f - i).

3.2- Tribo-electrification and adhesion behaviour of binary mixtures

3.2.1- Effect of polymer concentration

The acquisition of tribo-electric charge and surface adhesion of powder formulations can be affected by the component ratios in a binary powder mixture (Engers *et al.,* 2007; Murtomaa and Laine, 2000). Tribo-electric charging and adhesion experiments were carried out on cellulose ether: flurbiprofen powder blends with fixed polymer to flurbiprofen loading ratios of 0.5, 1, 2.5, 5, 10 and 15 w/w %. The charging and adhesion results show that the addition of increasing proportions of polymer has a significant impact ($p < 0.05$) on these properties; as the level of cellulose ethers increased from 0.5 to 15 %, the charge and surface adhesion was decreased. At 0.5 % polymer content, there is a slight decrease in the charge and surface adhesion of flurbiprofen with addition of A4M, F4M and E4M. With further increases in polymer concentration, the charge dissipation increases significantly due to the influence of polymer to drug ratio on the overall effective work function and surface resistivity of a bulk powder sample (Figure 3 and Table 3). Likewise, the charge reduction reached a plateau level

at 5 and 10 % and so further increases in polymer concentration only had a small impact on charge, however, the surface adhesion was further reduced (Table 3). Binary mixtures formed using polymers K4M, K15M and K100M were the lowest charging blends; the addition of 0.5% w/w of polymer halved the overall net charge on flurbiprofen. Moreover, at 15% polymer, the charge was neutralised completely and particle adhesion was also very low. The charge reduction is likely due to ordering of particles as particles of opposite charges adhered to each other as electrovalent bonds developed between drug and excipient powder particles due to an exchange of electrons. Additionally, there was a shift in polarity of charge from negative to positive at levels of 15% w/w for blends containing K15M and K100M, a phenomenon previously encountered for glucose/lactose mixtures (Murtomaa and Laine, 2000). In the present scenario, it can be assumed that the K15M and K100M have a lower work function and surface resistivity than flurbiprofen and the contacting surface (stainless steel). Thus, when the percentage of polymer is increased, the net surface resistivity and effective work function of powders is altered leading to a reduction and shift in polarity of electrostatic charge. As expected, such a significant charge reduction changes the classification from a high charging to a low charging category, and the impact of charge during powder handling will be reduced.

3.2.2- Effect of polymer particle size

The effect of polymer particle size on the propensity of charge and surface adhesion of cellulose ether: flurbiprofen blends during the contact electrification process against the stainless steel surface is shown in Figure 3 and Table 2. Charge and surface adhesion increased with the reduction in particle size regardless of concentration and polymer grade. An increase in particle size for the positively charging polymer provides more active sites on a single carrier particle for negatively charged flurbiprofen particles to attach, leading to an ordered

mixing which reduces the electrostatic charge and surface adhesion of powder particles. Furthermore, the particle size variation might also change the magnitude of effective work function of powder blends. These findings imply that manipulation of polymer particle size may aid reduction of electrostatic properties and adhesion of pharmaceutical powder mixtures.

3.3.3- Effect of polymer substitution ratio and molecular size (viscosity)

The chemical heterogeneity and molecular size of cellulose ethers can affect charging and surface adhesion due to variations in particle dynamics during the tribo-charging process. Hpo/Meo substitution ratios and the molecular size of cellulose ethers have a significant effect on the cellulose ethers:flurbiprofen mixtures (Figure 3 and 4). The overall net charge and surface adhesion decreased with an increase in Hpo/Meo substitution ratios (i.e. A>F>E>K) and molecular size (for K series); this was true for both particle size fractions. It is notable that as substitution ratio and molecular size increases, surface irregularities increase resulting in a more complex morphology, due to the difference in local atomic number and packing of molecular chains, as described earlier. Moreover, these changes can modify surface resistivity and the effective work function of powder blends, thus enabling cellulose ethers to show anti-static and anti-adhesive properties. Additionally, the agglomeration and stability of these powder mixtures is improved with more complex surface carrier particles compared with smooth surface particles (Saharan *et al*., 2008; Swaminathan and Kildsig, 2000).

3.4- Relationship between tribo-electric charging and particle surface adhesion

Table 2 shows the adhesion of polymer particles to the steel surface calculated as a ratio between the initial feed and the mass loss due to powder sticking. A reduction in adhesion is observed with a decrease in electrostatic charge on the particles. Figure 5 shows the

relationship between charge and surface adhesion for all binary mixtures having varying polymer particle size (90-150 µm and 150-250 µm) and concentration (0.5-15 % w/w). The electrostatic charge was spawned due to electron transfer from the polymer to flurbiprofen powder particles, as described earlier. A reduction in susceptibility towards tribo-electric charging is directly related to surface adhesion, with correlation coefficients ranging between 0.81-0.98 (Table 4). The A4M powder blends show a higher degree of correlation than others, while K100M blends were at the lower end of this series. The particle size distribution also has an impact on the correlation which tends to decrease with decreasing particle size.. The decrease in the particle size has engendered molecular and Van der Waals forces, as both depend on the distance between the contacting powder particles (Cross, 1987). The large surface area associated with a reduction in particle size reduced the distance between the powder particles thus giving rise to a higher intensity of operational forces during the experiments. The current study shows that electrostatic forces generated during the tribo-electrification process played a significant role during the surface adhesion phenomena of pharmaceutical powders. However, it is appreciated that the mechanism of particle adhesion is a complex process and other mechanisms may also be involved (Cowell, 2003; Donald, 1969).

4-Conclusion

The study revealed that particle size, chemical heterogeneity and molecular size of cellulose ethers all significantly impact = their charging and adhesion behaviour. For the API, the results show that charge generation, due to tribo-electrification processes, was significant and may give rise to surface adhesion, leading to flow, compaction and content uniformity problems. This may compromise the quality of the final dosage form during tabletting. An electrostatic charge-assisted ordering has been demonstrated to be an effective tool for the dissipation of charge on the API. The charge and adhesion were highly dependent on the concentration ($P <$

0.05), particle size, substitution ratios and molecular size of the cellulose ethers. The decrease in surface adhesion and charge dissipation of flurbiprofen powder mixtures is intuitively expected to improve its flowability and compaction which is expected to have a positive effect on the finished pharmaceutical dosage forms.

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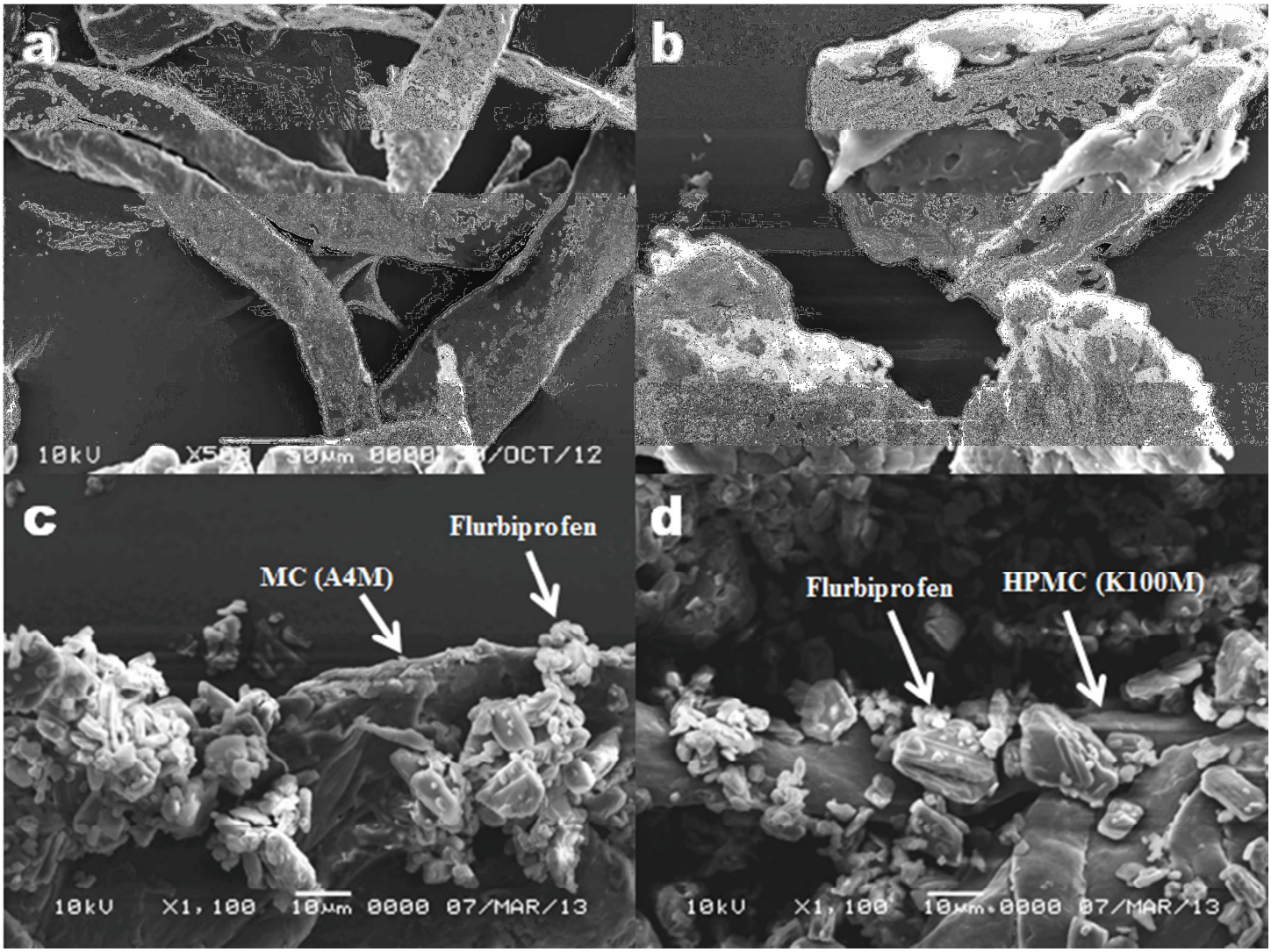

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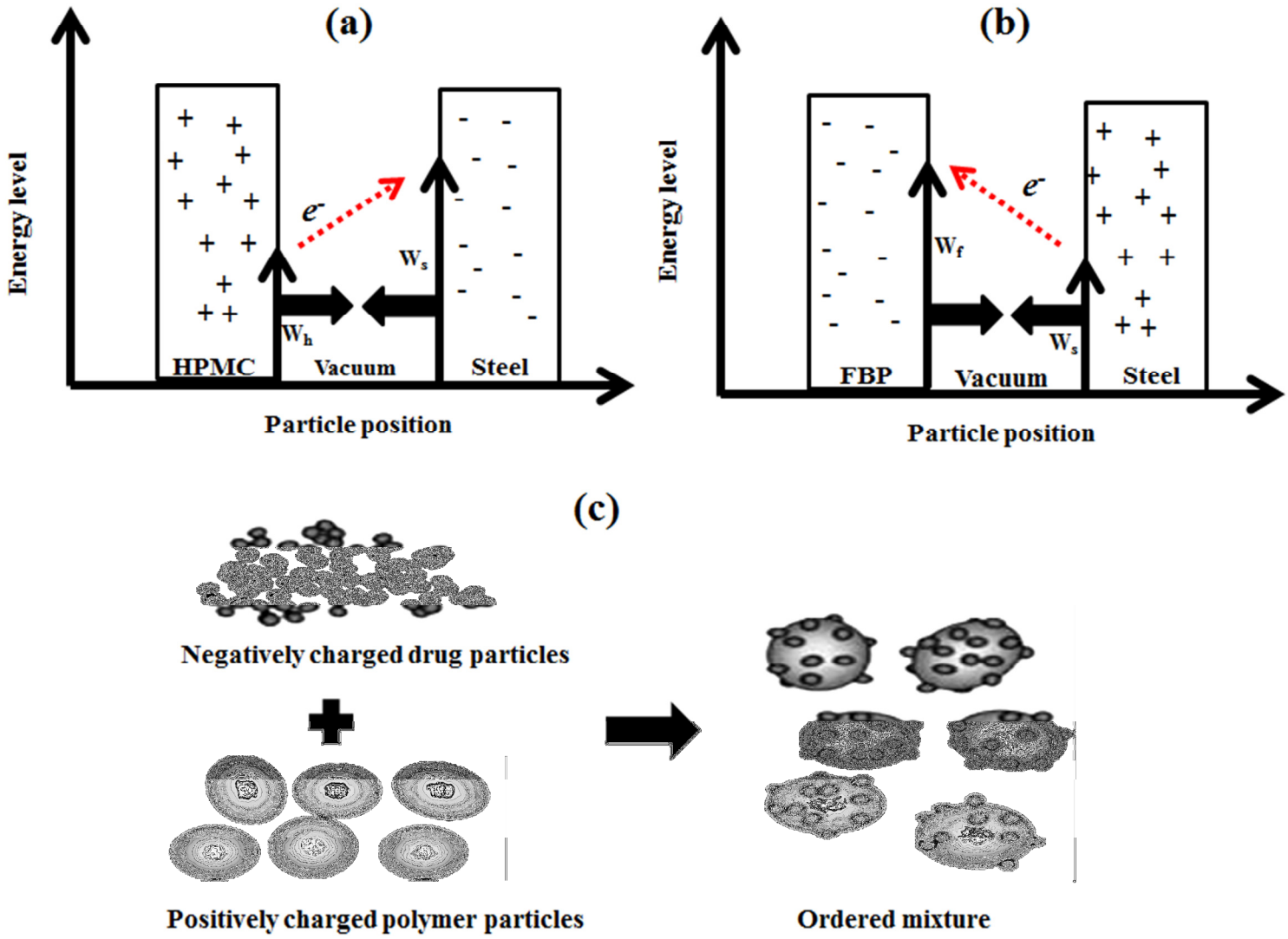

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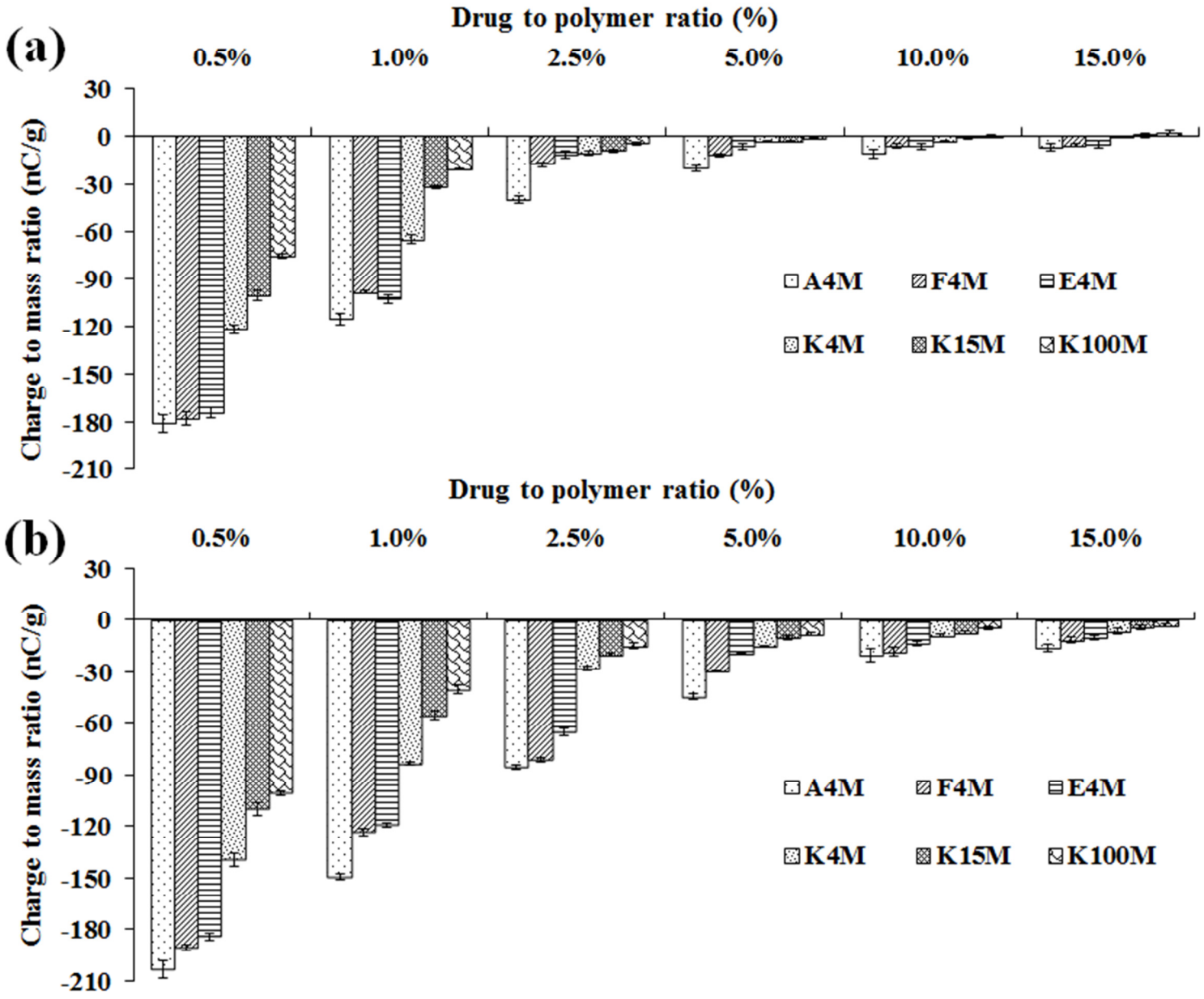
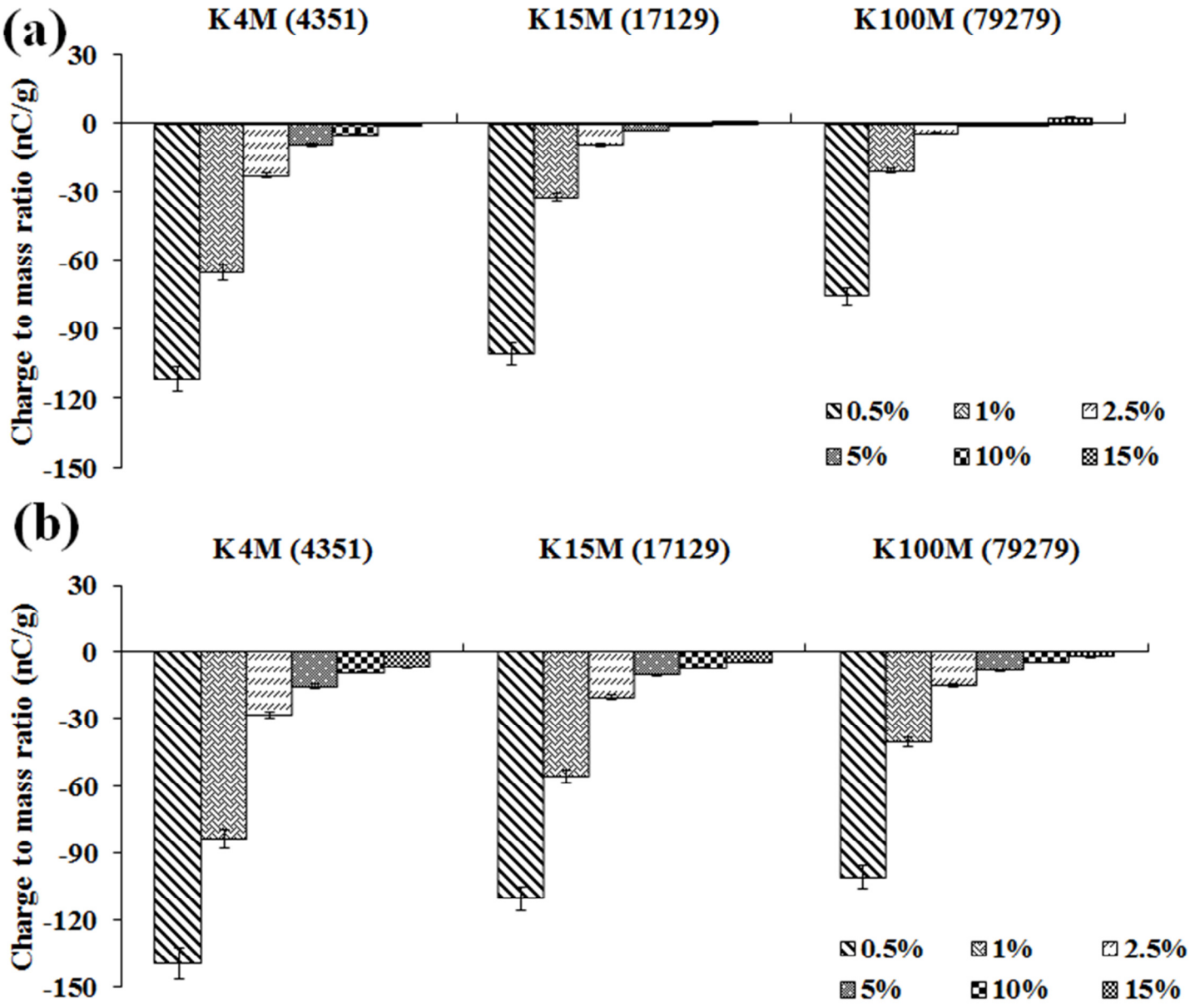


Figure 3. Effect of polymer concentration on the tribo-electric charging of cellulose ether:flurbiprofen powder mixtures; polymer particle size (a) 150 - 250 µm and (b) 90 - 150 µm, n=3.



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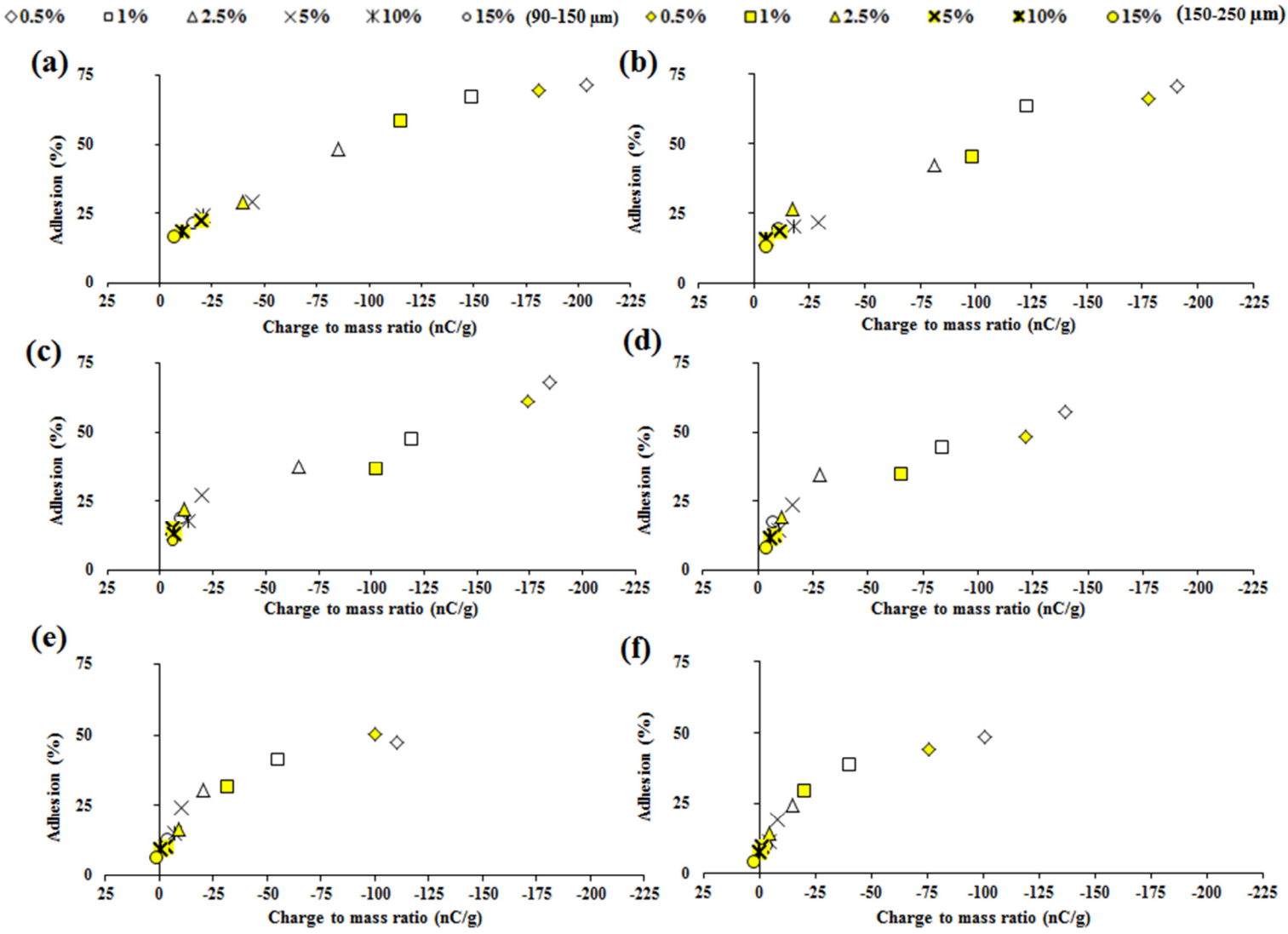

Figure 5. Effect of tribo-electric charge (nC/g) on surface adhesion (%), (a) A4M (b) F4M (c) E4M (d) K4M (e) K15M (f) K100M having polymer particle size 90-150 µm and 150-250 µm.

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	~86000
Methocel® F4M	28.1	6.7	0.238	34.8	4031	~90000
Methocel® E4M	29.0	8.3	0.286	37.3	3919	~92000
Methocel® K4M	22.3	8.5	0.381	30.8	4351	~88000
Methocel® K15M	22.3	9.0	0.403	31.3	17129	~125000
Methocel® K100M	22.5	8.9	0.395	31.4	79279	~215000

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

Table 2. Charge-to-mass ratio and percentage particle adhesion of polymers and flurbiprofen (standard deviation is shown in parentheses, n=3)

Material	Particle size	Charge to mass ratio (*Q/M*)	Adhesion (%)
Flurbiprofen	**38 – 63 µm**	-243.13 (13.25)	74.23 (4.32)
Methocel® A4M	**90 – 150 µm**	57.44 (2.81)	32.98 (2.12)
	150 – 250 µm	54.33 (2.21)	29.69 (1.89)
Methocel® F4M	**90 – 150 µm**	44.02 (1.32)	25.08 (2.23)
	150 – 250 µm	39.67 (3.14)	20.64 (0.99)
Methocel® E4M	**90 – 150 µm**	26.90 (2.64)	20.11 (1.55)
	150 – 250 µm	19.86 (1.15)	17.87 (1.23)
Methocel® K4M	**90 – 150 µm**	12.33 (2.23)	11.37 (1.11)
	150 – 250 µm	9.78 (3.69)	11.82 (2.55)
Methocel® K15M	**90 – 150 µm**	10.36 (2.15)	12.09 (1.12)
	150 – 250 µm	7.06 (1.68)	10.51(0.88)
Methocel® K100M	**90 – 150 µm**	4.23 (0.85)	5.59 (1.15)
	150 – 250 µm	3.94 (0.66)	7.93 (0.91)

Table 3. Adhesion (%) of polymer/ flurbiprofen powder mixtures (standard deviation in parentheses, n=3).

Polymer	Particle Size	Adhesion (%)					
		Polymer concentration (%)					
		0.5	1	2.5	5	10	15
Methocel® A4M	**90 – 150 µm**	71.5 (3.81)	67.1 (3.51)	48.5 (2.77)	28.9 (1.82)	24.1 (1.59)	21.4 (1.54)
	150 – 250 µm	69.7 (3.77)	58.1 (1.89)	29.2 (2.38)	22.4 (2.54)	18.2 (0.88)	16.3 (1.05)
Methocel® F4M	**90 – 150 µm**	70.8 (2.74)	63.4 (3.14)	42.3 (1.25)	21.9 (2.47)	20.2 (1.58)	19.4 (0.92)
	150 – 250 µm	66.3(3.55)	45.2 (2.02)	26.5 (2.34)	18.4 (3.25)	15.2 (2.21)	12.9 (1.09)
Methocel® E4M	**90 – 150 µm**	68.2 (3.88)	47.2 (1.46)	37.5 (1.4)	27.2 (2.21)	17.6 (2.17)	18.6 (1.06)
	150 – 250 µm	61.3 (3.24)	36.5 (1.69)	22.2 (2.54)	14.5 (1.37)	12.9 (1.54)	10.5 (1.15)
Methocel® K4M	**90 – 150 µm**	57.3 (1.85)	44.5 (0.88)	34.5 (1.27)	23.5 (2.88)	17.2 (0.56)	14.3(1.54)
	150 – 250 µm	48.1 (2.12)	34.5 (2.25)	19.2 (1.25)	12.3 (1.25)	11.1 (1.12)	8.0 (0.23)
Methocel® K15M	**90 – 150 µm**	47.3 (2.33)	41.2 (1.48)	30.5 (1.15)	24.3 (2.41)	15.1 (2.25)	12.6 (0.58)
	150 – 250 µm	50.2 (2.51)	31.5 (1.55)	16.5 (0.88)	10.2 (0.88)	9.5 (1.47)	6.5 (2.10)
Methocel® K100M	**90 – 150 µm**	48.5 (1.89)	38.3 (1.21)	24.5 (0.78)	19.3 (1.10)	11.5 (1.09)	9.8 (0.48)
	150 – 250 µm	44.2 (2.20)	29.3 (1.25)	14.1 (0.98)	9.2 (0.55)	7.3 (0.88)	4.2 (0.51)

Table 4. Relationship between tribo-electric charge and surface adhesion

Material	Correlation co-efficient (R^2)	
	Particle size (90-150 µm)	Particle size (150-250 µm)
A4M/FBP	0.959	0.980
F4M/FBP	0.956	0.973
E4M/FBP	0.974	0.961
K4M/FBP	0.913	0.955
K15M/FBP	0.815	0.940
K100MFBP	0.857	0.894

Supplementary data

Figure 1. SEM micrographs (a) F4M Premium (b) E4M Premium (c) K4M Premium (d) K15M Premium (e) Flurbiprofen (FBP) (f) F4M/FBP (g) E4M/FBP (h) K4M/FBP (i) K15M/FBP powder mixtures.

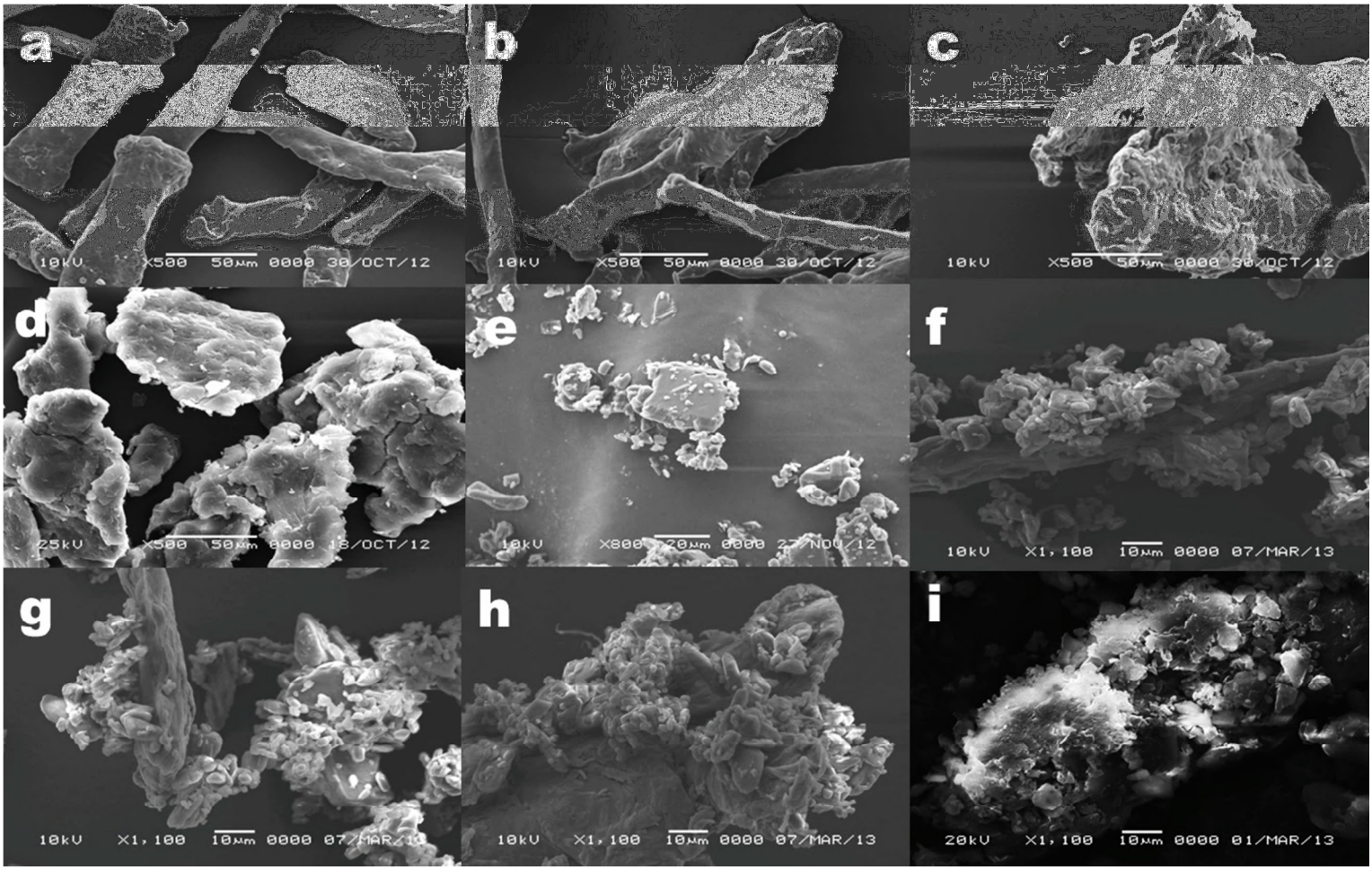

Figure 2, Effect of polymer substitution ratios on the tribo-electric charging of cellulose ether : flurbiprofen powder mixtures, (a) polymer particle size 150 - 250 µm and (b) 90 - 150 µm, (n=3; mean±s.d.)