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Characterisation of freeze-dried wafers and solvent evaporated films as potential drug delivery systems to mucosal surfaces

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ABSTRACT

Freeze-dried (lyophilised) wafers and solvent cast films from sodium alginate (ALG) and sodium carboxymethylcellulose (CMC) have been developed as potential drug delivery systems for mucosal surfaces including wounds. The wafers (ALG, CMC) and films (CMC) were prepared by freeze-drying and drying in air (solvent evaporation) respectively, aqueous gels of the polymers containing paracetamol as a model drug. Microscopic architecture was examined using scanning electron microscopy, hydration characteristics with confocal laser scanning microscopy and dynamic vapour sorption. Texture analysis was employed to investigate mechanical characteristics of the wafers during compression. Differential scanning calorimetry was used to investigate polymorphic changes of paracetamol occurring during formulation of the wafers and films. The porous freeze-dried wafers exhibited higher drug loading and water absorption capacity than the corresponding solvent evaporated films. Moisture absorption, ease of hydration and mechanical behaviour were affected by the polymer and drug concentration. Two polymorphs of paracetamol were observed in the wafers and films, due to partial conversion of the original monoclinic to the orthorhombic polymorph during the formulation process. The results showed the potential of employing the freeze-dried wafers and solvent evaporated films in diverse mucosal applications due to their ease of hydration and based on different physical mechanical properties exhibited by both type of formulations.

1. Introduction

Many wound dressings are available for treating wounds including hydrocolloids (e.g. carboxymethylcellulose), alginates, hydrogels, films and foam dressings. These have absorbent properties and are able to form gels upon contact with wound exudate. The main functional principle for these dressings is the provision and maintenance of a moist environment that promotes wound healing. There are five inter-related stages of wound healing (Schultz, 1999) as well as different types of wounds and one dressing cannot target every phase of healing or all wound types. In addition, no single dressing satisfies all the required characteristics for an 'ideal dressing' (Boateng et al., 2008). With the exception of alginate dressings, where calcium ions present are known to take active part in wound physiology such as blood clotting and inflammation (Thomas et al., 2000; Lansdown, 2002) most dressings play only a passive role in the wound healing process. There is a growing need for novel formulations with improved physical properties and containing pharmacological agents, which take active part in the wound healing process.

Film dressings are thin semi-permeable adhesive sheets made by drying polymeric solutions or gels of nylon or acrylic derivatives. Film based wound dressings have been available on the market for quite some time and have the advantage of being transparent, allow application to difficult areas such as joints due to their flexibility and do not require additional taping. Their key disadvantage is the collection of wound exudate under the dressing with the risk of maceration of healthy skin tissue. In addition, their tendency to fold up causes difficulty in handling during application. Freeze-dried (lyophilised) wafers on the other hand are relatively novel

Abbreviations: CMC, sodium carboxymethylcellulose; ALG, sodium alginate; DVS, dynamic vapour sorption; SEM, scanning electron microscopy; CLSM, confocal laser scanning microscopy; DSC, differential scanning calorimetry; TA, texture analyser.

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formulations prepared by freeze-drying of polymeric solutions or gels to yield solid porous structures that can easily be applied to suppurating wound surfaces (Matthews et al., 2003). Their physical architecture resembles those of foam dressing sheets which are made of porous polyurethane, sometimes with adhesive borders. Wafers provide a potential means of delivering pharmacological agents to wound surfaces to aid healing. They potentially, offer an advantage over other wound delivery systems such as semi-solid polymer gels, which have shorter residence times when applied to a suppurating wound (Matthews et al., 2005).

The physical properties of pharmaceutical formulations such as wound dressings critically influence characteristics that are acceptable to both patients and clinicians (Morgan, 2002). The properties that are characterised depend on factors such as the type of wound dressing and any secondary dressings that may be involved. Other factors include the nature of the surface to which the dressing will be applied and the purpose of the dressing, e.g. passive wound healing or dressing containing active ingredients (Boateng et al., 2008). The current approach to characterising wound dressings involve simple standard tests specified in Official publications such as European/US Pharmacopoeia, British Standards and American Standards for Testing and Materials. Examples include fluid handling properties, moisture vapour permeability, fluid affinity, water uptake and gelling properties (Gatti et al., 2004). However, these standard tests are based mainly on the structure of the dressing components and not on properties that affect their functional characteristics. In addition, because the tests are specified for a given dressing type (e.g. hydrocolloids), results obtained are not readily comparable with other dressings (e.g. alginates or hydrogels). Other physical properties that critically influence the performance of formulations for application to moist surfaces include tensile strength (films), hydration, bioadhesivity, rheological properties (gels and films), resistance to compressive forces (sheets) and drug release characteristics. The importance of these properties and the need for their characterisation has been reviewed (Boateng et al., 2008). The development, rheological measurements and effect of sterilisation and physical characterisation of freeze-dried wafers containing xanthan gum as drug delivery system for wound healing have been investigated (Matthews et al., 2006, 2008).

In addition, knowledge of such properties is of value in predicting the final properties of the formulation including drug release characteristics and physical appearance. For example ease of hydration and mechanical strength are important in selecting ideal materials to achieve good muco-adhesion and subsequently affect controlled drug delivery to moist surfaces. Formulations that form adhesive interactions with biological substrates have been reported to offer certain advantages for mucosal drug delivery including prolonged residence time and ease of application (Lawlor et al., 1999; Jones et al., 2003). Formulations designed for drug delivery to wound sites however, require a good balance between ensuring long residence time to deliver drugs and preventing damage to newly formed tissue. An excessively high force of adhesion between a dressing and wound surface or a hard, brittle dressing, can damage newly formed tissues during change of the dressing and application respectively. We have recently reported on the development and mechanical characterisation of solvent cast films as potential drug delivery systems to moist surfaces including wounds (Boateng et al., 2009a) and on the drug release characteristics of freeze-dried wafers and films prepared from sodium carboxymethylcellulose (Boateng et al., 2009b).

This paper describes the development, formulation and characterisation of the physical–mechanical properties of freeze-dried wafers (ALG and CMC) and solvent cast films (CMC) as potential drug delivery systems to wounds and other mucosal surfaces. Paracetamol has been incorporated into both formulations as a model drug. The formulations have been characterised for microscopic structure, hydration properties, water sorption–desorption and mechanical strength using scanning electron microscopy (SEM), confocal laser scanning microscopy (CLSM) and dynamic vapour sorption (DVS) and texture analysis respectively. In addition, differential scanning calorimetry (DSC) has been used to investigate polymorphic changes of the model drug occurring during formulation of the wafers and films. The data obtained from the characterisation has been used to compare (a) ALG and CMC freeze-dried wafers, (b) films and wafers prepared from CMC as well as (c) formulations containing different concentrations of polymer and the model drug (paracetamol).

2. Experimental

2.1. Materials

Sodium alginate (ALG) (Protanal LF10/60LS with high mannuronic acid chains was donated by FMC Biopolymer (Drammen, Norway). Protanal LF 10/60 LS exhibits flexible mechanical properties owing to higher mannuronic acid content (average guluronic/mannuronic ratio of 40:60). Sodium carboxymethylcellulose (CMC) (Blanose 7H4XF, high viscosity grade) was provided as a gift from Hercules Inc. (Virginia, USA) respectively. Sodium fluorescein, rhodamine, and paracetamol were purchased from Sigma (Gillingham, UK).

2.2. Preparation of freeze-dried wafers and solvent evaporated films

Initially, aqueous gels of ALG (1–5%, w/w) and CMC (0.5–3%, w/w) were prepared by dispersing the required amount (g) of polymer in the vortex of vigorously stirred distilled water maintained at a temperature of 90 °C (Boateng et al., 2009a). For paracetamol loaded gels, the drug was first dissolved in the hot distilled water (90 °C) and the CMC powder dispersed into the vortex of the vigorously stirred paracetamol solution to produce a uniform gel. The freeze-dried wafers were prepared by freeze-drying the gels (5 g) of ALG (1–5%, w/w) and CMC (0.5–3%, w/w) in a VirTis Advantage Freeze-Drier (VirTis Company Inc., Gardiner, NY, USA). This involved initially cooling samples from room temperature to −60 °C over a period of 7 h. The frozen samples were then heated in a series of thermal ramps to 25 °C under vacuum over a 10-h period. The solvent evaporated CMC films were prepared by pouring the aqueous gels into trays and dried by placing in sealed desiccators at relative humidity of 6% and temperature of 45 °C.

2.3. Texture analysis

The mechanical properties (resistance to deformation and ease of recovery) of the freeze-dried wafers were investigated by compressing on a Texture Analyser (TA) (Stable Microsystems Ltd., Surrey, UK) in compression mode. The probe deformed the sample at a speed of 0.2 mm/s to a given depth (0.2–3 mm) and withdrawn till it lost complete contact with the wafer. Ten ALG and CMC wafers (2%, w/w solution) were compressed at three different locations to a depth of 2 mm at a speed of 1 mm/s to determine the reproducibility in the response of the wafers to deformation by compression. The same settings were used to determine the effects of polymer (1–5%, w/w) and paracetamol (9.1–47.4%, w/w) contents on the force–time profiles during deformation by compression.

2.4. Confocal laser scanning microscopy (CLSM)

Disc-shaped freeze-dried wafers were prepared from CMC gels (0.5–3.0%, w/w) as described in Section 2.2 but with the addition

Table 1
Reproducibility in 'hardness' of ten freeze-dried wafers from 2% ALG and CMC compressed at three different locations to a depth of 2 mm at a speed of 1 mm/s, using 6 mm diameter stainless steel probe (standard deviations given in parentheses). The 'hardness' is peak resistance force of the wafers to deformation and corresponds to the maximum force attained in the Texture Analyser plot.

Wafers	Mean 'hardness' for compression at three positions on same wafer (*N*) (±s.d.)	
	ALG wafer (2%, w/w)	CMC wafer (2%, w/w)
1	21.7 (0.1)	6.8 (0.9)
2	23.4 (0.1)	7.7 (1.7)
3	22.8 (1.8)	7.9 (1.4)
4	20.0 (0.6)	8.9 (1.8)
5	19.6 (0.4)	6.9 (1.2)
6	20.1 (0.4)	6.8 (0.9)
7	20.4 (1.0)	5.7 (1.2)
8	19.8 (0.3)	7.4 (1.2)
9	22.3 (2.0)	5.8 (0.5)
10	21.5 (1.1)	7.4 (1.2)

of 1 mL of 0.6 g/L sodium fluorescein to the gel before freeze-drying. The yellow coloured freeze-dried discs were placed and compressed in a device designed to ensure consistent depth of sample for microscopical examination. Samples were mounted in a device which allowed hydration of the wafers from one side only whilst mounted on the microscope stage. Radial ingress of rhodamine stained water into the samples was analysed using a Bio-Rad MRC 1024ES Confocal Laser Scanning Imaging System (Bio-Rad Ltd., Hemel Hempstead, UK) coupled to a Nikon upright microscope (Nikkon Instruments Inc., New York, USA) using the argon laser line at 488 nm. Scans were performed during initial hydration at the edge of the wafers with a 10× 0.25 NA objective every 5 s over an area of 1400 sq μm.

2.5. Scanning electron microscopy (SEM)

Freeze-dried wafers and solvent evaporated films were fixed in place by means of double sided copper electrical tape and gold-coated in a Polaron SC515 SEM Coating System (Bio-Rad sputter coater, Bio-Rad Ltd., Hemel Hempstead, UK). SEM images were obtained using a Phillips SEM 515, with a spot size of 320 Å and 12 kV intensity at magnifications of 100–800.

2.6. Dynamic vapour sorption (DVS)

The moisture sorption–desorption properties of the freeze-dried wafers and solvent evaporated films containing 0–41.2% (w/w) of paracetamol were determined. The formulations (approximately 20 mg) were subjected to an initial drying stage from ambient to 0% relative humidity to ensure that percent changes in weight during the sorption–desorption cycle were on a dry weight basis. The dried sample was subsequently subjected to a stepwise increase and decrease in relative humidity from 0 to 95% and 95 to 0% respectively at 25 °C. The total weight of water absorbed (sorption phase) and lost (desorption phase) was recorded.

Table 2
Peak forces (*N*) obtained by compressing freeze-dried ALG wafers prepared from 1% to 5% (w/w) solutions to depths of 2 mm, at speed of 1.0 mm/s using 6 mm diameter stainless steel probe.

Concentration of solution used to prepare wafers (%, w/w)	Peak resistance force at 2 mm depth (*N*) (±s.d.)
1	6.1 (0.5)
2	20.6 (1.0)
3	45.7 (3.3)
4	68.6 (3.3)
5	93.7 (10.1)

Table 3
Peak force values attained and changes in wafer dimensions with increasing depth of compression (deformation) for ALG and CMC wafers (2%, w/w solution) at a compression speed of 0.2 mm/s, using 6 mm diameter stainless steel probe.

Depth of compression a (mm)	ALG				CMC			
	Mean peak force (*N*) (±s.d.)	Relaxation distance (mm) *b* (±s.d.)	Ratio of compression: relaxation distance (recovery ratio) (±s.d.)	Compaction (mm) *a* − *b* (±s.d.)	Mean peak force (*N*) (±s.d.)	Relaxation distance (mm) *b* (±s.d.)	Ratio of compression: relaxation distance (recovery ratio) (±s.d.)	Compaction (mm) *a* − *b* (±s.d.)
0.2	1.9 (0.2)	0.2 (0.01)	1.1 (0.04)	0.01 (0.01)	1.38 (0.1)	0.19 (0.01)	1.06 (0.08)	0.01 (0.01)
0.4	3.8 (0.2)	0.4 (0.01)	1.1 (0.02)	0.04 (0.01)	2.48 (0.2)	0.33 (0.01)	1.21 (0.06)	0.07 (0.01)
0.8	9.9 (0.1)	0.6 (0.01)	1.3 (0.02)	0.19 (0.01)	3.95 (0.1)	0.60 (0.03)	1.33 (0.11)	0.20 (0.01)
1.0	17.1 (2.1)	0.7 (0.01)	1.4 (0.02)	0.29 (0.01)	4.47 (0.2)	0.70 (0.14)	1.43 (0.29)	0.30 (0.14)
2.0	30.4 (0.2)	1.1 (0.07)	1.9 (0.06)	0.95 (0.07)	8.65 (0.3)	1.02 (0.02)	1.96 (0.04)	0.98 (0.03)
3.0	41.6 (0.1)	1.1 (0.01)	2.8 (0.02)	1.91 (0.01)	14.92 (0.2)	1.08 (0.01)	2.78 (0.04)	1.92 (0.01)

Table 4
Changes in dimensions with increasing depth of compression (deformation), for CMC wafers prepared from 2% (w/w) solution containing increasing amounts (9.1–47.4%, w/w) of paracetamol (1 mm/s, 2 mm, 6 mm diameter stainless steel probe).

Paracetamol content (%, w/w)	Relaxation distance (mm) b (±s.d.)	Ratio of compression: relaxation a:b (±s.d.)	Compaction $a-b$ (±s.d.)	Relaxation compared to 2% CMC
9.1	1.1 (0.1)	1.9 (0.3)	0.9 (0.1)	1.1
16.7	1.0 (0.2)	1.8 (0.4)	1.0 (0.2)	1.0
23.1	0.9 (0.1)	2.2 (0.3)	1.1 (0.1)	0.9
33.3	0.9 (0.2)	2.2 (0.3)	1.1 (0.2)	0.9
41.2	0.8 (0.2)	2.4 (0.5)	1.2 (0.2)	0.8
47.4	0.7 (0.1)	2.7 (0.3)	1.3 (0.1)	0.7

2.7. Differential scanning calorimetry (DSC)

DSC was performed using pure paracetamol crystals, recrystallised paracetamol (freeze-dried and dried in desiccators) as well as paracetamol contained in the freeze-dried wafers and solvent evaporated films. The wafers and films used for the DSC study were prepared from 2% (w/w) CMC gels containing 16.7% (w/w) of paracatamol on a dry weight basis. The pure and recrystallised paracetamol crystals were initially heated in 40 μl aluminium pans with pierced lids on the differential scanning calorimeter (TC 15 TA, Metler Toledo Ltd., Leicester, UK) from 25 to 200 °C at a rate of 10 °C/min. Paracetamol contained in the wafers and films was subjected to a similar heating profile.

3. Results

3.1. Texture analysis

Table 1 shows the reproducibility of ten different wafers for 2% ALG and CMC wafers when compressed to a depth of 2 mm at three different locations. Table 2 also shows the changes in 'peak resistance to deformation' ("hardness") for ALG wafers (1–5%, w/w) also compressed to 2 mm. The results show an increase in resistance to compressive deformation with increasing concentration of polymer. The changes in resistance to compression (peak force) and relaxation of wafers after removing the deforming force, with increasing depth of compression are shown in Table 3. The effect of paracetamol content on the ability of the wafers to recover to their original dimensions after compression to different depths is summarised in Table 4.

3.2. Confocal laser scanning microscopy (CLSM)

Representative images captured from the CLSM showing the ingress of water into the freeze-dried wafers are shown in Fig. 1. The fluorescein stained wafer is coloured green in the image, whilst the advancing rhodamine stained water appears red. (For interpretation of the references to colour in the text, the reader is referred to the web version of the article.) The rate of water ingress (hydration rate) into the wafers having different polymer contents are summarised in Table 5. The slowing down of hydration with increasing polymer concentration from the confocal study confirmed our

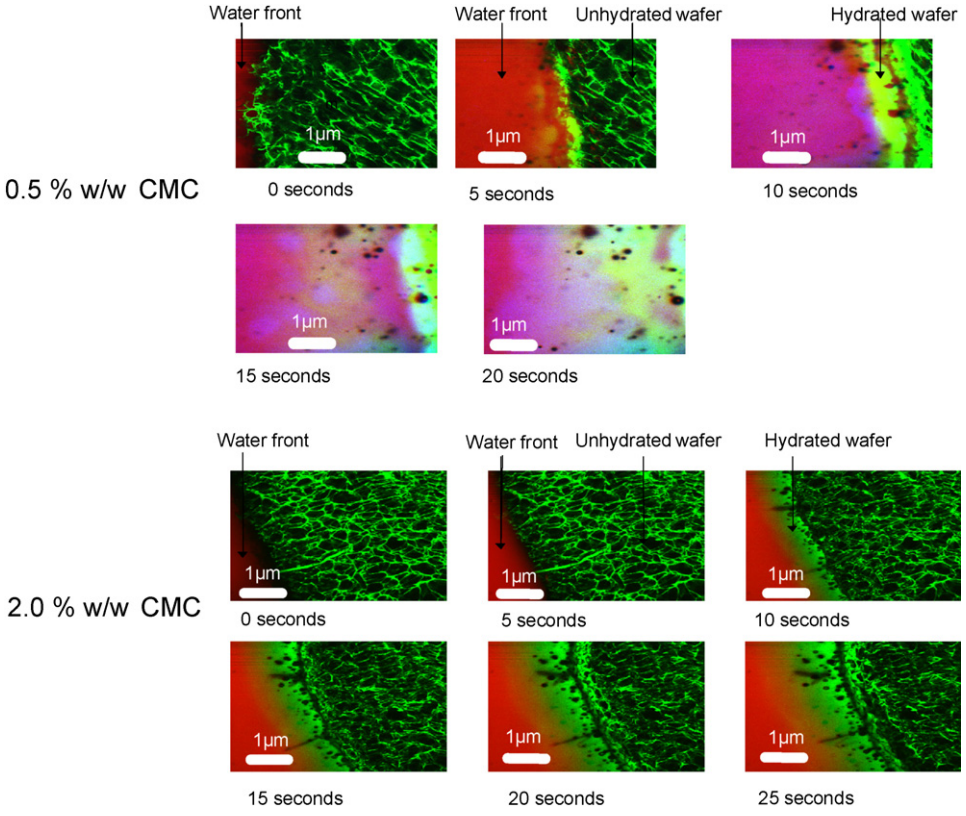

Fig. 1. CLSM images of CMC freeze-dried wafers prepared from 0.5% (w/w) and 2.0% (w/w) solutions at 0–25 s following addition of water, showing the rate of water ingress into the wafers with time.

Table 5
Assessment of hydration from the CLSM showing the initial rate of water ingress into freeze-dried formulations measured over 10 s.

CMC wafer (%, w/w)	Rate of hydration (μm/s) (±s.d.)	Rates compared to 2% CMC wafer
0.5	114.2 (1.6)	2.5
1.0	61.3 (3.9)	1.3
1.5	57.4 (3.3)	1.3
2.0	45.5 (3.9)	1.0
2.5	34.1 (0.5)	0.8
3.0	11.8 (0.4)	0.3

findings from an earlier publication (Boateng et al., 2009b) that polymer hydration rate was the most important factor affecting drug release from both wafers and films.

3.3. Scanning electron microscopy (SEM)

SEM images comparing freeze-dried wafers prepared from ALG and CMC are shown in Fig. 2. CMC wafers formed a porous interconnecting network of polymeric strands having several circular shaped pores, whilst ALG wafers also formed an interconnecting network, but which appeared sponge-like with elongated and fewer pores. The scanning electron micrographs showing the differences in the drug loading capacity between the wafers and films (from 2%, w/w solution) are shown in Fig. 3.

3.4. Dynamic vapour sorption (DVS)

A representative DVS trace for a formulation taken through a full sorption-desorption cycle, is shown in Fig. 4. The results of the moisture sorption and desorption data for the wafers and films are summarised in Table 6. Increasing paracetamol content resulted in a decrease in water content from 12% (0% drug content) to 3% (41.2%, w/w of drug) for both formulated wafers and films. In addition, there was a decrease in the total amount of water absorbed with increasing paracetamol content in the wafers (120–113%) and films (119–84%) after the first DVS cycle from 0 to 95% RH.

3.5. Differential scanning calorimetry

Representative DSC thermograms of pure paracetamol and that contained in CMC freeze-dried wafers and solvent evaporated films are shown in Fig. 5. The pure and recrystallised paracetamol showed

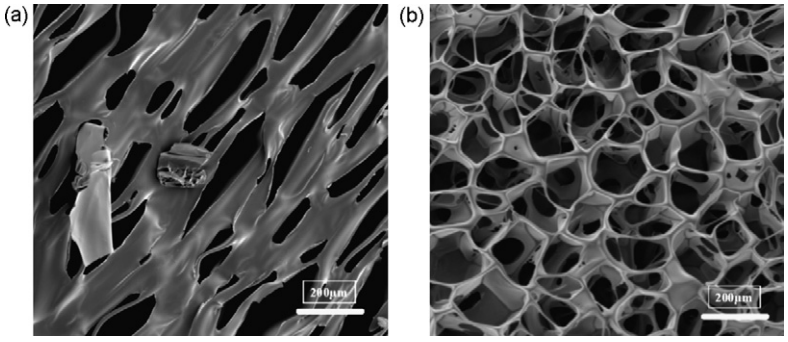

Fig. 2. SEM images of freeze-dried: (a) ALG wafers having elongated pores and (b) CMC wafers showing spherically shaped porous network. Both type of wafers were prepared by freeze-drying 2% (w/w) aqueous solutions of ALG and CMC.

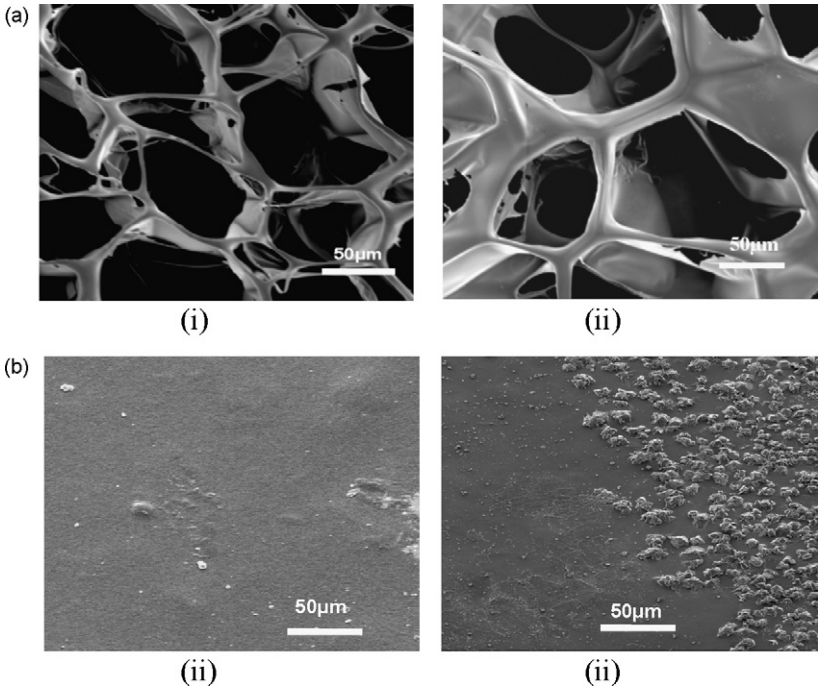

Fig. 3. Representative SEM images showing the differences in surface morphology, drug disposition and loading capacity between CMC: (a) freeze-dried wafers and (b) solvent evaporated films. Images labelled (i) contained no paracetamol and those labelled (ii) contained 9.1% (w/w) paracetamol of the total dry weight.

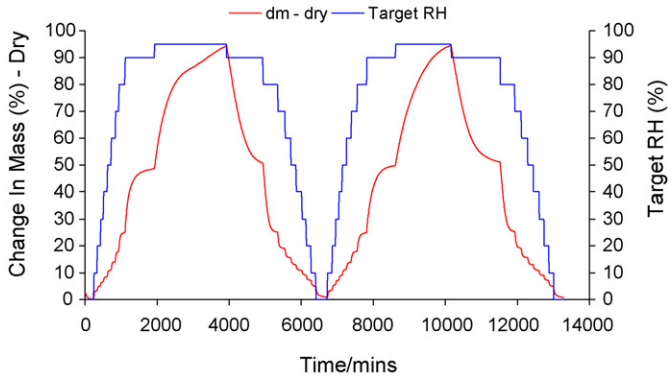

Fig. 4. Typical DVS trace of wafer exposed to relative humidity between 0 and 95% (sorption phase) and then from 95 to 0% (desorption).

Table 6
Summary of DVS moisture sorption by CMC wafers and films containing 0–41.2% (w/w) of paracetamol. Total water absorbed is expressed as a percentage of the initial dry weight and based on one DVS cycle. The initial water content was determined by measuring the percent weight loss after the initial drying stage. This was achieved by reducing the humidity from ambient conditions to 0% humidity till constant weight.

Paracetamol content of formulations (%, w/w)	Initial water content (estimated after initial drying to constant weight) at 0% humidity) (%)	Maximum water absorbed (%)
Wafers		
0	13.5	120.4
23.1	7.4	113.2
33.3	4.4	110.3
41.2	2.7	94.2
Films		
0	12.4	119.4
23.1	5.3	103.7
33.3	5.2	98.2
41.2	3.3	84.0

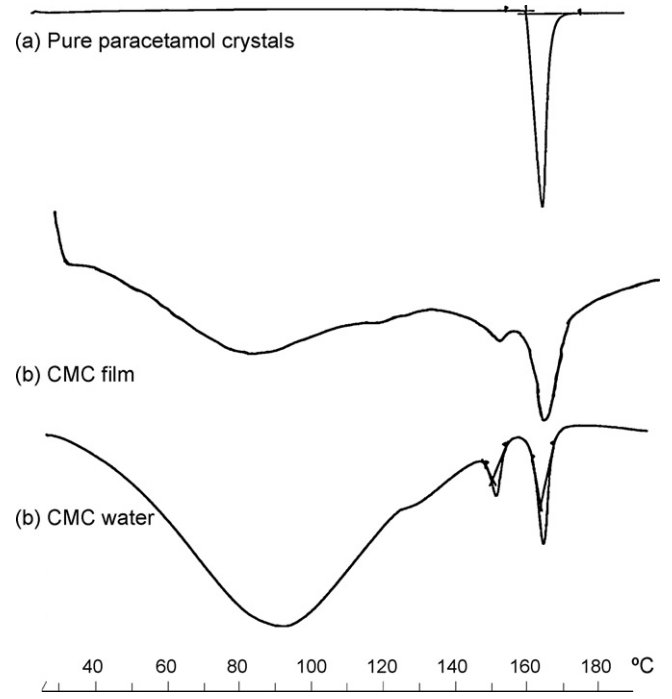

Fig. 5. Melting peaks as seen on DSC plots of: (a) pure paracetamol (169 °C) and paracetamol polymorphs at temperatures of 169 °C (form I) and 157 °C (form II) present in (b) CMC films and (c) CMC wafers.

a single peak with onset melt temperature of 169 °C corresponding to the monoclinic (form I) polymorph in all cases. However, two peaks were observed in both the freeze-dried wafers and solvent evaporated films that corresponded to the monoclinic (169 °C) and orthorhombic (157 °C) forms of paracetamol.

4. Discussion

The results generally showed that the physical characteristics of both the freeze-dried wafers and solvent evaporated films were determined by (a) the type of polymer (ALG, CMC) and (b) concentration of polymer and drug. The differences in the number, size and shape of pores between ALG and CMC wafers could account for the differences in their mechanical strength measured on the Texture Analyser. Jones et al. (1996, 1997) found that the resistance of hydroxypropylethylcellulose and CMC gels to compression increased steadily with increased polymer concentration. The increase in resistance to compressive deformation and lower recovery of original shape after removal of the compressive force was possibly a consequence of reduction in porosity when compressed to greater penetration depths and more intimate contact of the polymer chains. The events occurring involved increase in resistance to compression from initial contact until the peak force when the given depth of compression was attained. The terms "compaction index" and ratio between '*a*' and '*b*' (Table 3) give an indication of how well the wafers relaxed and re-gained their original shape after deformation. A ratio close to one (low penetration depths) indicates reversibility upon removal of the compressive deformation force. At low depths of compression, the wafers re-gained their original dimension as shown by the apparent symmetry in the force distance profile ($b \simeq a$). This symmetry was however, lost as the depth of compressive deformation increased as evidenced by the increasing difference between *b* and *a*. At higher depths of compression, the wafers did not recover and showed a gradual increase in recovery ratio and at 3 mm compression distance, a sharp increase in ratio indicated permanent deformation of the wafers. These defined parameters are critical, as significant changes to wafer dimensions could affect properties such as its pore size. Such variations if large enough may result in significant changes in hydration, swelling and possibly drug release characteristics. However, this will need to be further investigated.

The results of the confocal microscopy study indicated that the rate of hydration of the CMC freeze-dried wafers and its subsequent hydration were determined by the amount of polymer present. These observations have significant influence on important formulation properties such as drug release characteristics (Boateng et al., 2009b). The differences in the surface morphology and drug disposition within the freeze-dried wafers and solvent evaporated films from the SEM images is quite important in explaining differences between their physical characteristics such as physical appearance, brittleness, drug loading and hydration rate. Whilst wafers could hold up to 47.4% of paracetamol without being deformed (i.e. maintained their shape compared to 0% drug loading), the corresponding films, were highly brittle, wrinkled and deformed with recrystallised paracetamol visibly present on the film surface beyond 9.1% drug loading. This can be attributed to the fact that the freezing stage during freeze-drying essentially set the initial gel height and therefore the final product has a volume similar to that of the original gel poured. This characteristic of freeze-dried systems could be employed in fast dissolving oral formulations where high doses are incorporated and rapidly released and absorbed in the oral cavity, along the oesophagus as well as in the stomach. The higher drug loading capacity of the freeze-dried wafers may stem from the fact that at low levels of paracetamol concentration, glass solution (amorphous formation) occurred resulting in most of the drug being incorporated completely into the wafer during freeze-drying.

The films on the other hand collapsed during the drying process for film formation, thereby presenting a significantly reduced volume for the drug loaded into the gel originally.

The decrease in the water sorption with increasing paracetamol in the DVS study (Table 6) may be due to less surface area of polymer available due to paracetamol recrystallised on the surface of the films and the strands that comprise the wafers. It may also reflect the fact that the distribution of drug between the amorphous polymer and its free crystal form is different and will require further investigation. In addition, the wafers absorbed more water during the DVS cycle than the corresponding films which can be attributed to the differences in the physical structures of the porous wafers and the dense non-porous films (Fig. 3). We have previously reported that such differences between the physical structures of the wafers and films resulted in significant differences in their drug release characteristics (Boateng et al., 2009b).

The presence of two melt peaks from DSC analysis of paracetamol contained in the wafers and films suggests polymorphism of the drug within the two types of formulations with some of the original single polymorph (form I, 169 °C) converted to another known polymorph (form II, 157 °C) (Di Martino et al., 1996). The melt peaks for paracetamol contained in the films tended to shift from the expected 157 and 169 °C because of a practical problem of the pieces of film not having proper contact with the base of the pan. As a result, the two melt peaks were broad and in some cases appeared to merge. This could be improved by preparing the films in the aluminium sample pans to improve contact and therefore heat transfer.

Boldyreva et al. (2004) have noted that "the stability relationship in respect to temperature of the polymorphs I and II is monotropic with the form I being the most stable at temperatures below its melting point of 169 °C". They suggested further based on isobaric conditions that "only solid-state transformations from the orthorhombic modification II into the monoclinic form I are thermodynamically allowed". Capes and Cameron (2007) have reported that certain polymers in solution suppress the formation of the metastable form II of paracetamol. The mechanism involved the polymers affecting the evaporation process of the solution, by disrupting solvent flows at sites on the edge of drops, where the metastable crystals would normally form. However, these reported cases seem to be contradicted by our DSC findings. It has been reported that monoclinic form I and orthorhombic form II are stable phases at ordinary temperatures and high pressures (Espeau et al., 2005). Some of the processes and materials that have been reported to cause transitions between these two forms include milling, compression, freeze-drying, melting, polymer additives such as agar, HPMC, and PVP (Femi-Oyewo and Spring, 1994). Other hydrophilic polymers such as PVA have been reported to be adsorbed unto paracetamol crystals during recrystallization thus altering the structural orientation of some of the crystals to yield other polymorphic forms (Di Martino et al., 1997). In the present study, it is possible that the CMC caused changes in the crystal form of paracetamol converting the monoclinic to the orthorhombic form. Given the fact that freeze-drying of the polymer gel could cause amorphous paracetamol to be incorporated into the polymer matrix, the transition may also be the result of some amorphous conversion that has recrystallised. However, this will require further investigation as the current data cannot support a definite amorphous-crystalline transformation resulting in the formation of the orthorhombic (metastable) polymorph.

5. Conclusions

Characterisation of the two different formulation types (wafers and films) using various techniques showed marked differences in their physical properties which is expected to impact on their performance characteristics. The mechanical strength and hydrating ability (moisture sorption) of the freeze-dried wafers depended largely on the amount of polymer present and to a limited extent on the amount of drug present. The porous nature of freeze-dried wafers confers the advantage of higher water absorption rate and drug loading capacity over the thin and denser solvent evaporated films. A key finding of the current study is the partial conversion of monoclinic polymorph of paracetamol to the metastable orthorhombic form and the preservation of this metastable polymorph. This observation can be attributed to the polymer (CMC) used to prepare the formulations rather than the freeze-drying or air drying process for wafers and films respectively. The transitions observed seem to counter the well publicised monotropic property of paracetamol polymorphism and suggests that other factors may be involved that allow the conversion of form I to the metastable form II.

The principal implication of these findings lie with the potential application of the more novel freeze-dried wafers as drug delivery systems to suppurating wound surfaces where large quantities of exudates are produced. They are also applicable for use in delivering large doses of drug via other mucosal routes such as the buccal mucosa.

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