Drug Development and Industrial Pharmacy, 2012; 38(1): 47–54
© 2012 Informa Healthcare USA, Inc.
ISSN 0363-9045 print/ISSN 1520-5762 online
DOI: 10.3109/03639045.2011.590496

RESEARCH ARTICLE

Comparison of the *in vitro* release characteristics of mucosal freeze-dried wafers and solvent-cast films containing an insoluble drug

Joshua S. Boateng[1], Kerr H. Matthews[2], Anthony D. Auffret[3], Mike J. Humphrey[3], Gillian M. Eccleston[4], and Howard N. Stevens[4]

[1]Department of Pharmaceutical, Chemical and Environmental Sciences, University of Greenwich at Medway, Kent, UK, [2]School of Pharmacy, The Robert Gordon University, School Hill, Aberdeen, UK, [3]Pfizer Limited, Sandwich Kent, UK, and [4]Department of Pharmaceutical Sciences, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

Abstract
Drug release characteristics of freeze-dried wafers and solvent-cast films prepared from sodium carboxymethylcellulose have been investigated and compared. *In vitro* drug dissolution studies were performed using an exchange cell and drug release was measured by UV spectroscopy at 272 nm using distilled water. The dissolution profiles of hydrochlorothiazide from the wafers and films were compared by determining the rates of drug release, estimated from the % release versus time profiles and calculating their difference (f_1) and similarity (f_2) factors. The effects of drug loading, polymer content and amount of glycerol (GLY) (films) on the drug release characteristics of both formulations were investigated. Both the wafers and films showed sustained type release profiles that were best explained by the Korsmeyer–Peppas equation. Changes in the concentration of drug and GLY (films) did not significantly alter the release profiles whilst increasing polymer content significantly decreased the rate of drug release from both formulations. The rate of release was faster from the wafers than the corresponding films which could be attributed to differences in the physical microstructure. The results show the potential of employing both formulations in various mucosal drug delivery applications.

Keywords: Carboxymethylcellulose, drug dissolution, hydrochlorothiazide, mucosal delivery, release mechanism

Introduction

Drug dissolution studies have become a standard means of evaluating the performance of different solid dosage forms, the most common being tablets and capsules. Factors affecting the release of drugs from polymer matrix systems include drug solubility, drug concentration and particle size[1]. For drug release by a purely diffusional mechanism, the drug first dissolves and then diffuses through the swollen gel layer into the dissolution medium[2]. In swellable-erodible systems, release characteristics depend on other factors apart from drug dissolution and diffusion (that is usually the rate-determining step). For an erosion-controlled mechanism, the diffusional path length is small and dissolution of the matrix is the rate-limiting step for drug release[3–5]. This scenario is most likely to occur for drugs of low aqueous solubility, at high loadings or for situations in which the matrix rapidly dissolves[6]. A drug with low solubility is more likely to exhibit drug release due to erosion because solid drug particles may exist in the hydrated layer near the eroding front[7,8].

Freeze-dried wafers are relatively novel formulations (compared to films) used for various applications including fast dissolving oral formulations[9], wound healing drug delivery[10,11] and nasal drug delivery[12,13]. They are produced by freeze-drying aqueous gels of various

Address for Correspondence: Joshua Boateng, Department of Pharmaceutical, Chemical and Environmental Sciences, School of Science, University of Greenwich at Medway, Central Avenue, Chatham Maritime, Kent, UK. Tel.: +44 (0) 208 331 8980. Fax: +44 (0) 208 331 9805. E-mail: j.s.boateng@gre.ac.uk, joshboat@hotmail

(Received 10 March 2011; revised 14 May 2011; accepted 18 May 2011)

hydrophilic polymers, resulting in a highly porous polymer network which readily hydrates upon contact with dissolution medium. Solvent-cast films on the other hand have been used over a longer period of time, but have gained renewed interest in recent years owing to their unique properties such as bioadhesion and portability. Films have also been used as wound dressings[14], for buccal mucosal delivery[15] and as fast dissolving oral strips[16]. In more advanced applications, films have been proposed for delivering proteins via buccal mucosa[17]. The use of polymers for controlled delivery of a model soluble drug (paracetamol) from freeze-dried wafers and solvent-cast films has been discussed in a previous article[18].

This paper investigates the dissolution and release of hydrochlorothiazide (HCT) as a model insoluble drug from freeze-dried wafers and solvent-cast films. The effect of drug loading, polymer content and glycerol (GLY) content (films) on the release profiles of HCT from sodium carboxymethylcellulose (CMC) wafers and films was investigated. In addition, the release rates of drug from both wafers and films have been calculated and compared.

Materials and methods

Materials

Sodium CMC (Blanose 7H4XF Food Grade) was obtained from Hercules, CA. Sodium hydroxide, standard phosphate buffers (pH 4, 7, 10) GLY and HCT, were all purchased from Sigma (Gillingham, UK); HCT is a diazide used as a diuretic in the management of mild to moderate hypertension and usually administered with other drugs. It is a white crystalline powder that is practically insoluble in water (1.10 mg/mL) and classed as a low solubility and low permeability drug according to the Biopharmaceutics Classification System, BCS[19,20].

Standard calibration and pH-solubility curves

Stock solutions of HCT (0.5 mg/mL) in distilled water and 0.1 M sodium hydroxide were prepared in duplicate. Different volumes of each stock solution were diluted to 100 mL to yield seven calibration solutions ranging from 0.5 to 2.50 mg/100 mL. The λ_{max} for HCT was determined by scanning the most concentrated of the calibration solutions between 200 and 400 nm. The absorbencies of these solutions were determined at 272 nm (water) and 274 nm (0.1 M sodium hydroxide) using 1 cm quartz cuvettes with a Helios Alpha Thermospectronic UVA 093227 UV spectrophotometer (Helios Alpha, England, UK). The standard curve was obtained by plotting the concentration of the solutions against absorbance.

The solubilities of HCT were determined at different pH (2, 4, 6, 8 and10) using buffer solutions at 37°C and from the pH-solubility profile a suitable pH (dissolution medium) was chosen for drug dissolution studies. Excess of HCT (110 mg for pH 2–6, 170 mg for pH 8–10) was continuously shaken in 50 mL of the appropriate buffer using a shaking incubator set to 37°C for 48 h. Five milliliter of supernatant was sampled from each mixture, filtered into 250 mL volumetric flasks and the volume made up to 250 mL with the appropriate buffer (to prevent possible precipitation or further dissolution of HCT). Five milliliter of the resulting solutions were again diluted with 0.1 M sodium hydroxide to fall within the calibration range and their absorbances measured at 274 nm, using 0.1 M sodium hydroxide as reference solution. The concentrations were computed from the standard equation for HCT dissolved in 0.1 M sodium hydroxide and subsequently the solubilities at the above pH values.

Preparation of wafers and films

Aqueous gels of CMC (0.5–3%, w/w) were initially prepared by dispersing the required amount (g) of polymer in the vortex of a vigorously stirred suspension of HCT (90°C). For plasticised gels, the required amount of GLY was first dissolved in water before HCT and polymer were added. Five gram of gel was poured into the wells of polystyrene culture (six multi-well) plates (diameter 34.8 mm) for each formulation. The freeze-dried wafers were prepared by freeze-drying gels contained in the six multi-well plates using a VirTis Advantage Freeze-Drier (VirTis Company Inc., Gardiner, NY) over a 25 h period (from 25°C to–60°C and then back to 25°C). The solvent-cast films were prepared by drying the gels in desiccators (48–72 h at a relative humidity of 6% and temperature of 45°C). Three distinct formulations were prepared to investigate the effects of (a) HCT (b) CMC and (c) GLY (films) concentration on the drug dissolution and release characteristics of the wafers and films (Table 1). The wafers and unplasticised films for determining the effect of drug concentration each contained 100 mg of CMC and 0.25–2.5 mg of HCT (~0.25–2.44% w/w of the total dry weight).

In vitro drug release studies

The *in vitro* dissolution and release properties of HCT in wafers and films were investigated using a diffusion cell (manufactured in house by Strathclyde university workshop) containing 125 mL of distilled water at 37°C[18]. The diffusion cell is based on the design of Cornaz Gudet *et al*[21] and consists of donor and receiver compartments with sampling ports. The inner diameter (35 mm) of the donor compartment is such as to allow the wafers and films to fit readily. It also has a small platform all round the inner circumference on which the wire mesh sits. The whole wafer (diameter 34.8 mm, thickness ~ 4 mm) or film (diameter 34.8 mm, thickness <1 mm) as prepared was placed on the wire mesh at the bottom of the donor compartment of the diffusion cell such that the underside of the formulation was just wet by the dissolution medium present in the receiver compartment. At given intervals (10-min intervals till 90 min, 30-min intervals till 240 min and every hour till 420 min), 5 mL of solution was sampled from the receiver compartment and replaced with fresh distilled water also maintained at 37°C to maintain

Table 1. Composition of the wafers and films for investigating effect of HCT, CMC and GLY (films) concentration on drug release characteristics. Formulations labelled as (Ref) were those selected as references for comparing the dissolution curves of the different formulations (cf. Table 6).

(a) Formulations (prepared from 2% w/w CMC solutions) containing increasing amounts of HCT. (NB: The films contained no glycerol).

Content of HCT of total dry weight (% w/w)	Weight of HCT per wafer and film (mg)	Weight of CMC per wafer and film (mg)	Weight of glycerol per film (mg)
0.25	0.25	100	—
0.50	0.50	100	—
0.99 (Ref)	1.00	100	—
1.47	1.50	100	—
1.96	2.00	100	—
2.44	2.50	100	—

(b) Formulations (wafers and films) containing increasing amounts of CMC but fixed contents of HCT and glycerol. (NB: The films contained glycerol).

CMC content of solution used (% w/w)	Weight of HCT per wafer and film (mg)	Weight of CMC per wafer and film (mg)	Weight of glycerol per film (mg)
0.5	1.0	25	100
1.0	1.0	50	100
1.5	1.0	75	100
2.0 (Ref)	1.0	100	100
2.5	1.0	125	100
3.0	1.0	150	100

(c) Films prepared from 2% w/w CMC solutions containing increasing amounts of glycerol but fixed content of HCT.

Ratio of GLY:CMC (by weight)	Weight of HCT per film (mg)	Weight of CMC per film (mg)	Weight of glycerol per film (mg)
0:1 (Ref)	1.0	100	0
1:1	1.0	100	100
3:2	1.0	100	150
2:1	1.0	100	200

constant volume. Where necessary, the sampled solution was diluted with distilled water to fall within the range of the UV standard calibration curve. Experiments were carried out in six replicates for each formulation. The drug released was measured by UV spectroscopy at a wavelength of 272 nm. The percent cumulative release was calculated and plotted against time, taking into consideration the 5 mL of solution which was sampled and replaced with fresh distilled water. Water was chosen as the dissolution medium based on initial pH-solubility measurements (see pH solubility of HCT section)

Drug release kinetics

The kinetics of HCT release from the wafers and films was determined by finding the best fit of the dissolution data (% release against time) to four kinetic models i.e. Korsmeyer–Peppas, Higuchi, zero order and first order equations. The effect of formulation variables (drug loading, CMC content and GLY (films) content), on the release kinetics of HCT were also investigated.

Comparison of release profiles

Dissolution profiles for the various formulations and variables under investigation were compared using the modified Moore and Flanner[22] equations (1 and 2) by calculating the difference (f_1) and similarity (f_2) factors. Reference formulations used in calculating the difference (f_1) and similarity (f_2) are highlighted in Table 1. Sampling time which corresponds to the amount of drug dissolved in that time period (e.g. $t_{50\,\mathrm{min}}$) was also used to characterise and compare drug release profiles.

$$f_1 = \frac{\sum_{j=1}^{n} \left| R_j - T_j \right|}{\sum_{j=1}^{n} R_j} \times 100 \quad (1)$$

$$f_2 = 50 \times \log \left\{ \left(1 + (1/n) \sum_{j=1}^{n} \left| R_j - T_j \right|^2 \right)^{-0.5} \right\} \times 100 \quad (2)$$

Results

Calibration curve and pH solubility of HCT

Linear calibration graphs were obtained for HCT in both distilled water ($y = 650.38x$; $R^2 = 0.9998$) and 0.1 M sodium hydroxide ($y = 516.24x$; $R^2 = 0.9996$). Because the drug was dissolved in buffers at different pH values, final solutions for solubility measurements were prepared with 0.1 M sodium hydroxide to ensure that all the solutions were at the same pH to avoid possibility of precipitation during UV measurements. This was the reason for plotting the calibration curve for HCT in 0.1 M sodium hydroxide. The solubility of HCT remained constant at 1.10 mg/mL between pH 2–6 and then increased sharply to 2.39 mg/mL at pH 10 (Figure 1). Therefore freshly prepared distilled water (pH 5–6) was chosen as the dissolution medium and

a wavelength of 272 nm used for all subsequent UV absorbance measurements during drug dissolution studies.

Release of HCT from wafers

The percentage cumulative release profiles of HCT from CMC wafers at different levels of drug concentration are shown in Figure 2A. Wafers containing 0.99% w/w of HCT appeared to produce the fastest release rate, releasing 50% of the initial amount of drug present by 50 min while those containing 0.25% w/w HCT showed the slowest release profile with $t_{50\%}$ of ~88 min (Table 2). The change in drug dissolution profiles from wafers containing increasing concentration of polymer is shown in Figure 2B. The release rates of HCT from these wafers, obtained from the linear portions (first 60% of release) of the dissolution curves are summarised in Table 3. The first 60% of release was chosen for estimating the release rates as most of the dissolution curves were generally linear within the 0–60% range.

Release of HCT from films

Figure 3A shows the dissolution profiles of CMC films containing different amounts of HCT. Films containing 1.96% w/w of HCT released the drug fastest, while those containing 0.25% w/w HCT released the drug slowest. The release profiles of plasticised films containing fixed amounts of GLY and HCT but varying amounts of CMC are shown in Figure 3B. The time to 50% release ($t_{50\%}$) from both films and wafers showing the effect of HCT and polymer content are summarised in Tables 2 and 3. Figure 4 shows the drug dissolution profiles from CMC films prepared from 2% w/w solutions containing 0.99% w/w of HCT and varying amounts of GLY. There was no significant change in release profiles and rates with increasing GLY content.

Kinetic mechanism and comparison of release profiles

Fitting of experimental drug dissolution data to four kinetic models (zero order, first order, Higuchi and Peppas power equation) showed that the Peppas power equation provided the best fit to the release data. The release data fitted to the Peppas power equation are summarised in Tables 4 and 5. The results of fitting dissolution data to zero order, first order and Higuchi models are not shown in Tables 4 and 5 due to low R^2 values indicating non-linear fit. The f_1 and f_2 values for the various formulations are shown in Table 6. The data from Tables 3–5 show that drug release was generally faster from the wafers than their corresponding films.

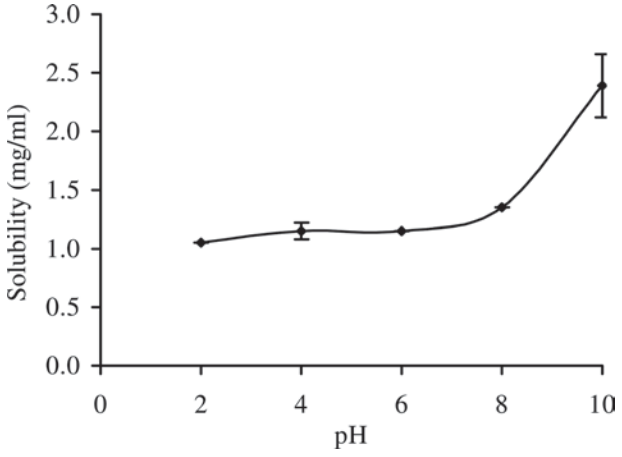

Figure 1. pH-solubility curve for HCT dissolved in buffer solutions ($n=2$).

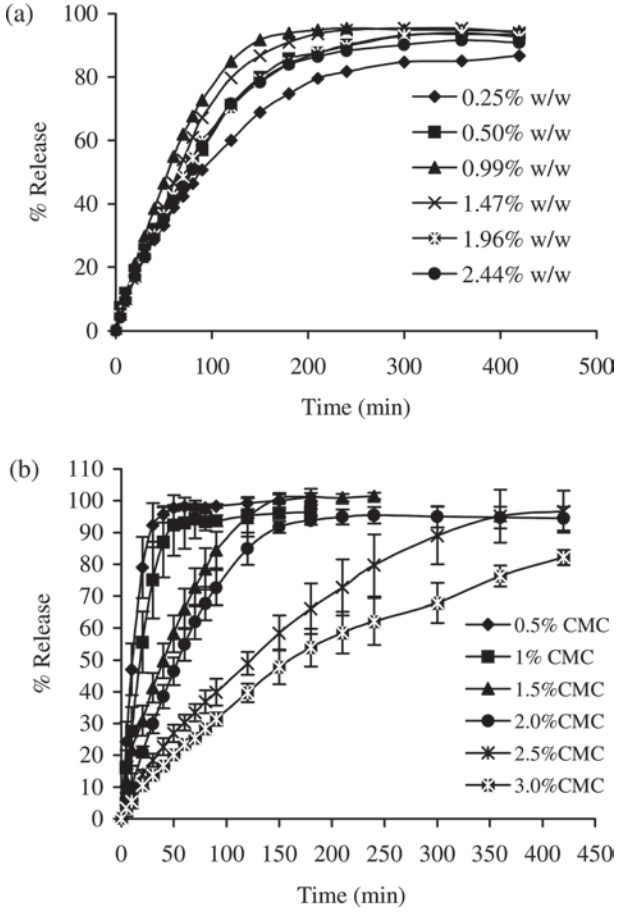

Figure 2. (A) Percent cumulative release profile for HCT from CMC wafers showing the effect of increasing drug content on the release (2% w/w solution, 37°C, $n=6$); (B) Effect of polymer content on the dissolution release profiles of HCT (0.99%w/w) from CMC wafers ($n=6$).

Table 2. Effect of HCT content on the time to 50% release ($t_{50\%}$) from CMC wafers and unplasticised films (2% w/w solution, 37°C, $n=6$) (cf. Figures 3A and A).

	Mean $t_{50\%}$ (min) (±SD)	
Drug content (% w/w)	Wafers	Films
0.25	88.0 (36.3)	123.2 (38.2)
0.50	70.2 (13.3)	82.5 (21.8)
0.99	74.3 (17.4)	101.2 (28.3)
1.47	86.0 (22.3)	107.3 (27.1)
1.96	72.3 (20.9)	103.8 (29.2)
2.44	71.5 (9.5)	105.8 (16.4)

Discussion

The wafers and films consisted of a uniform mix of CMC and HCT which produced matrix systems. Films for investigating the effects of polymer content also contained GLY as plasticizer which yielded more flexible films with increased thickness, therefore rendering them easier to remove from the casting containers without damage[23]. Dissolution and drug release profiles of HCT from the wafers and films were of the sustained release type. This was similar to those observed for two water soluble drugs, sodium salicylate[24] and paracetamol[18] from similar CMC matrices.

Table 3. Effect of polymer content on the time to 50% release ($t_{50\%}$) from CMC wafers (0.99% w/w) and plasticised films ($n=6$) (cf. Figures 3B and B).

CMC content (% w/w)	Mean $t_{50\%}$ (min) (±SD)	
	Wafers	Films
0.5	11.0 (1.8)	11.8 (2.4)
1.0	18.0 (4.3)	20.3 (3.3)
1.5	40.0 (5.7)	45.0 (6.3)
2.0	54.3 (5.6)	55.3 (5.0)
2.5	119.3 (15.3)	125.5 (13.1)
3.0	174.7 (27.3)	183.0 (26.8)

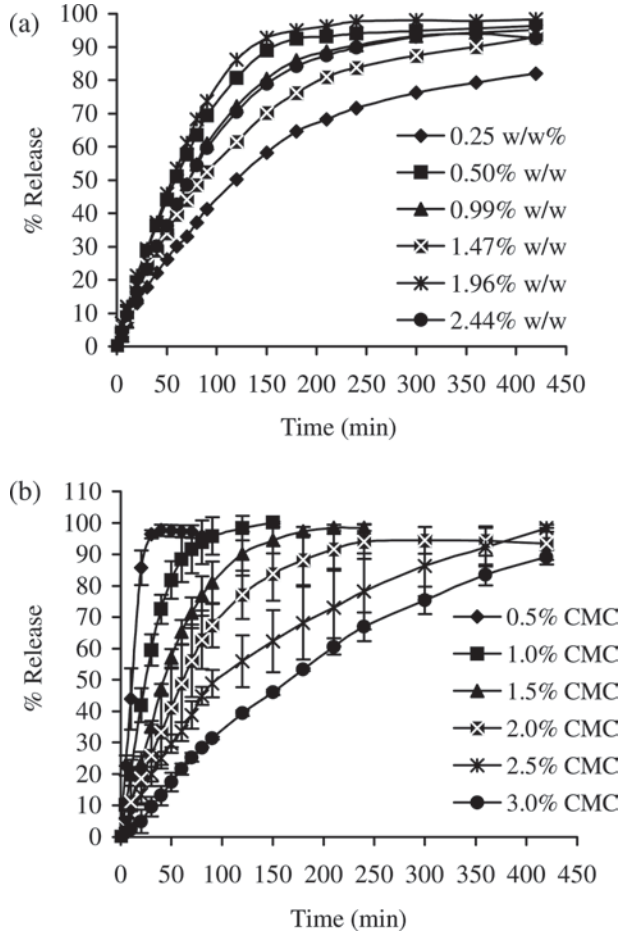

Figure 3. (A) Effect of drug loading on dissolution profile of HCT from CMC films (2% w/w solution $n=6$); (B) Effect of CMC content on *in vitro* dissolution release profiles of HCT (1 mg/film) from plasticised (100 mg GLY) CMC films ($n=4$) at 37°C.

Changes in the HCT concentration in both wafers and films had no significant effect on the release profiles and rates of release. This was indicated by the difference (f_1) and similarity (f_2) factors (Table 6) which showed that the dissolution profiles for these formulations were all similar. These observations indicate that factors other than drug solubility and mass transfer (diffusion) phenomena were involved in the mechanism of drug release. The main factors suggested for this study include hydration, swelling and erosion properties of the formulations, which depend largely on the type and amount of excipient[25], the proportion and grade of polymer[26] and polymer hydration characteristics[27]. The formulations for determining the effect of HCT loading all contained the same proportion of CMC by weight. They therefore produced similar sustained release profiles as a result of the viscous gel formed after initial hydration (Figures 3A and 4A). Gel erosion also played an important role owing to the water solubility of sodium CMC which can allow the delivery of drug together with the dissolved polymer to the dissolution medium. Drug diffusion through the swollen gel layer and its subsequent erosion are generally regarded as the rate-limiting steps of drug release from such matrices[28]. Relaxation that occurs during swelling and erosion, have been cited as the reasons for the deviations of release profiles from the square root of time kinetics[29].

However, changing dissolution profiles with varying amounts of CMC were observed for both the wafers and films (Figures 2B and 3B). Formulations prepared from 0.5 to 1.5% w/w CMC solutions released their content of drug relatively faster than those prepared from 2.0 to 3.0% w/w solution. Wafers and films with low CMC content (0.5 to 1.5% w/w) hydrated and disintegrated very rapidly during dissolution and the swelling phase lasted for a shorter period of time. The formulations containing higher amounts of CMC on the other hand hydrated and swelled more slowly to produce a gel, which slowly disintegrated. These mechanically stronger gels released drug at a controlled rate by diffusion through the gel and subsequent dissolution of this gel resulting in sustained

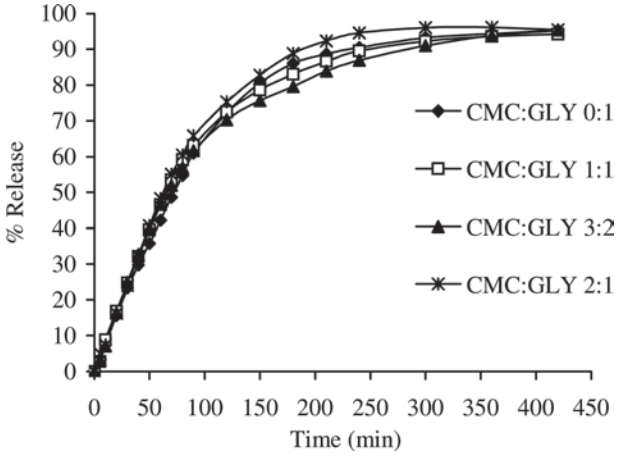

Figure 4. Drug dissolution profiles of CMC films showing the effect of GLY content on release of HCT (0.99% w/w).

Table 4. Fitting of results of the experimental dissolution release data to the Korsemeyer–Peppas kinetic equation for CMC wafers and films (2% w/w) containing different amounts of HCT (0.25–2.44% w/w), K_p values are mean release rates (% min^{-n}) of six replicate samples, R^2 is the correlation coefficient (coefficient of variation), and gives an indication of linearity of the plot, n is the release exponent.

	Wafers			Films		
HCT content (% w/w)	K_p (% min^{-n})	n	R^2	K_p (% min^{-n})	n	R^2
0.25	2.02	0.73	0.992	1.61	0.80	0.990
0.50	2.09	0.73	0.998	0.83	1.01	0.990
0.99	1.78	0.93	0.994	1.54	1.07	0.988
1.47	1.44	0.84	0.990	1.55	0.79	0.995
1.96	1.71	0.84	0.992	1.11	0.89	0.994
2.44	1.36	0.86	0.991	0.99	0.91	0.990

Table 5. Fitting of results of the experimental dissolution release data to the Korsmeyer–Peppas kinetic equation for CMC wafers and plasticized films (0.5–3.0% w/w of CMC) containing 0.99% w/w of HCT. K_p values are mean release rates (% min^{-n}) of six replicate samples, R^2 is the correlation coefficient, n is the release exponent.

Polymer content	Wafers			Films		
(% w/w)	K_p (% min^{-n})	n	R^2	K_p (% min^{-n})	n	R^2
0.5	6.40	0.82	0.990	5.01	0.94	0.995
1.0	4.99	0.93	0.992	2.03	1.00	0.998
1.5	4.24	0.67	0.994	1.17	1.10	0.994
2.0	1.91	0.93	0.994	0.86	1.04	0.994
2.5	1.76	0.70	0.995	0.71	0.85	0.994
3.0	0.89	0.78	0.992	0.27	1.04	0.980

Table 6. Similarity and difference factors for dissolution profiles of CMC wafers and films for determining the effect of drug loading and CMC content (% w/w) as well as glycerol content of films (GLY:CMC ratio by weight) on dissolution profiles. These were relative to the reference formulations highlighted as 'Ref'.

		Similarity factor (f_2)		Difference factor (f_1)	
Components	Variable (% w/w)	Wafers	Film	Wafers	Film
HCT content	0.25	20.6	23.7	41.6	41.4
	0.50	11.6	9.6	52.6	60.6
	0.99	Ref	Ref	Ref	Ref
	1.47	6.1	8.7	65.8	61.7
	1.96	11.9	14.6	52.6	52.6
	2.44	13.7	1.7	50.1	90.7
CMC content	0.5	75.7	161.6	20.4	15.8
	1.0	49.6	82.1	26.8	27.5
	1.5	16.8	41.9	50.8	39.1
	2.0	Ref	Ref	Ref	Ref
	2.5	27.3	20.0	34.1	43.4
	3.0	42.2	38.3	26.6	30.1
Glycerol content (GLY:CMC)	0:1	—	Ref	—	Ref
	1:1	—	6.7	—	68.0
	3:2	—	4.4	—	74.7
	2:1	—	5.3	—	71.9

release profiles. It is also important to note that the total weight of the formulations increased with increasing polymer concentration (Table 1B). The wafers and films containing high polymer concentrations will therefore be denser, with reduced surface area which explains their slower rate of hydration.

The release of HCT was generally faster from the wafers than from the corresponding films. This was particularly true at the initial 60% of release (Tables 4 and 5). These differences in release rate could be attributed to the differences between the physical properties of the wafers and films, which affect their initial rate of hydration and swelling. These differences in physical microstructure between the wafers and films, from scanning electron micrographs have been reported previously[30]. The wafers which were porous in nature, allowed a faster rate of water ingress and therefore faster polymer hydration rate than the dense and continuous films[23]. Therefore the rate of swelling and subsequent dissolution and diffusion of HCT from the resulting gel was higher for the wafers than

the films. This was especially true during the initial stages of drug release. Another possibility for increased dissolution rate in wafers compared to the films could be the formation of amorphous HCT induced by freeze-drying. There were no DSC (differential scanning calorimetry) and XRD (x-ray diffraction) experiments to prove this hypothesis, however, it has been reported that increased in dissolution rates of freeze-dried HCT mixed with β-cyclodextrin did not result from the formation of solid inclusion complex as was expected[31].

Fitting of the dissolution data to the four kinetic models and evaluation of the R^2 values showed that the Kormeyer–Peppas model explained the release data most accurately. Drug release from swellable matrices is usually complex and tends to be governed by both diffusion and erosion mechanisms. Analysis of the experimental data using this equation, and interpretation of the release exponents (n), provides a better understanding of the mechanisms controlling release and the balance between them. The release exponents generally varied from 0.67 to 0.93 (cylindrical wafers) and 0.79 to 1.11 (planar thin films). These values of n (which are dependent on the physical dimension of the drug loaded formulation) show an anomalous (non-Fickian) transport for most of the formulations[32]. This suggests that both diffusion of HCT in the hydrated CMC gel combined with erosion of the gel controlled drug release. However, the release exponents were mostly <0.89 for the wafers and >0.89 for the films and may suggest that gel erosion plays a more significant role in wafers whilst swelling plays a more significant role in drug release from the films[33].

These formulations (wafers and films) have been shown previously to have the potential for use as mucosal drug delivery systems[10,30,34–36]. Therefore, these differences observed between the two formulation types as well as the effect of other formulation variables (polymer content) make them suitable for various mucosal applications. The faster release rate of drug from wafers and films containing low polymer levels make them suitable candidates for fast dissolving tablets and oral thin films. On the other hand, wafers and films containing higher amounts of the polymer which hydrate at a slower rate will be better suited for controlled release applications both in the buccal cavity and on wound surfaces.

Conclusions

The HCT dissolution results for the wafers and films followed a sustained type release profile determined by matrix swelling, drug diffusion through the swollen matrix and eventual erosion of the matrix. Generally, the rate of HCT release was faster from the wafers than the corresponding films. The rate of drug release from the wafers (porous) and films (non-porous) was independent of the drug concentration but was affected significantly by the amount of polymer present. These differences present the possibility of using these formulations in different mucosal applications.

Acknowledgements

The authors are grateful to Pfizer Ltd., UK, for funding this project and to Hercules Inc. for donating carboxymethylcellulose.

Declaration of interest

This project was funded by Pfizer UK. The authors report no declarations of interest.

References

1. Grassi M, Grassi G. (2005). Mathematical modelling and controlled drug delivery: matrix systems. Curr Drug Deliv, 2:97–116.
2. Kaunisto E, Marucci M, Borgquist P, Axelsson A. (2011). Mechanistic modelling of drug release from polymer-coated and swelling and dissolving polymer matrix systems. Int J Pharm, doi:10.1016/j.ijpharm.2011.01.021.
3. Giunchedi P, Maggi L, Conte U, La Manna A. (1993). Linear extended release of a water-insoluble carbamazepine, from erodible matrices. Int J Pharm, 94:15–22.
4. Lu Z, Chen W, Hamman JH. (2010). Chitosan–polycarbophil interpolyelectrolyte complex as a matrix former for controlled release of poorly water-soluble drugs I: *in vitro* evaluation. Drug Dev Ind Pharm, 36 (5), 539–546.
5. Vueba ML, Batista de Carvalho LA, Veiga F, Sousa JJ, Pina ME. (2004). Influence of cellulose ether polymers on ketoprofen release from hydrophilic matrix tablets. Eur J Pharm Biopharm, 58:51–59.
6. Corvelyn S, Remon, JP. (1998). Formulation of a lyophilized dry emulsion tablet for the delivery of poorly soluble drugs. Int. J. Pharm, 166:65–74.
7. Bettini R, Catellani PL, Santi P, Massimo G, Peppas NA, Colombo P. (2001). Translocation of drug particles in HPMC matrix gel layer: effect of drug solubility and influence on release rate. J Contr Rel, 70:383–391.
8. Skoug JW, Mikelsons MV, Vigneron CN, Stemm NL. (1993). Qualitative evaluation of the mechanism of release of matrix sustained release dosage forms by measurement of polymer release. J Contr Rel, 27:227–245.
9. Corvelyn S, Remon JP. (1997). Formulation and production of rapidly disintegrating tablets by lyophilisation using hydrochlorothiazide as a model drug. Int J Pharm, 152:215–225.
10. Matthews KH, Stevens HNE, Auffret AD, Humphrey MJ, Eccleston GM. (2005). Wafers for wound healing. Int J Pharm, 289:51–62.
11. Matthews KH, Stevens HN, Auffret AD, Humphrey MJ, Eccleston GM. (2006). Gamma-irradiation of lyophilised wound healing wafers. Int J Pharm, 313:78–86.
12. McInnes FJ, Thapa P, Baillie AJ, Welling PG, Watson DG, Gibson I et al. (2005). *In vivo* evaluation of nicotine lyophilised nasal insert in sheep. Int J Pharm, 304:72–82.
13. McInnes FJ, O'Mahony B, Lindsay B, Band J, Wilson CG, Hodges LA et al. (2007). Nasal residence of insulin containing lyophilised nasal insert formulations, using gamma scintigraphy. Eur J Pharm Sci, 31:25–31.
14. Boateng JS, Matthews KH, Stevens HN, Eccleston GM. (2008). Wound healing dressings and drug delivery systems: a review. J Pharm Sci, 97:2892–2923.
15. Jug M, Becirevic-Lacan M, Bengez S. (2009). Novel cyclodextrin-based film formulation intended for buccal delivery of atenolol. Drug Dev Ind Pharm, 35:796–807.
16. Cilurzo F, Cupone IE, Minghetti P, Buratti S, Gennari CG, Montanari L. (2011). Diclofenac fast-dissolving film: suppression of bitterness by a taste-sensing system. Drug Dev Ind Pharm, 37:252–259.

17. Colonna C, Genta I, Perugini P, Pavanetto F, Modena T, Valli M, Muzzarelli C, Conti B. (2006). 5-methyl-pyrrolidinone chitosan films as carriers for buccal administration of proteins. AAPS PharmSciTech, 7:70. (Available at http://www.aapspharmscitech.org)
18. Boateng JS, Matthews KH, Auffret AD, Humphrey MJ, Stevens HN, Eccleston GM. (2009). *In vitro* drug release studies of polymeric freeze-dried wafers and solvent-cast films using paracetamol as a model soluble drug. Int J Pharm, 378:66–72.
19. Amidon GL, Lennernäs H, Shah VP, Crison JR. (1995). A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res, 12:413–420.
20. Guidance for Industry. (2000). Dissolution Testing of Immediate Release Solid Oral Dosage Forms U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER).
21. Cornaz Gudet A.-L, DeAscentis A, Colombo P, Buri P. (1996). *In vitro* characteristics of nicotine microspheres for transnasal delivery. Int J Pharm, 129:175–183.
22. Moore JW, Flanner HH. (1996). Mathematical comparison of dissolution profiles. Pharm Tech, 20, 64–74.
23. Boateng JS, Stevens HN, Eccleston GM, Auffret AD, Humphrey MJ, Matthews KH. (2009). Development and mechanical characterization of solvent-cast polymeric films as potential drug delivery systems to mucosal surfaces. Drug Dev Ind Pharm, 35:986–996.
24. Sebert P, Bourny E, Benghalem A, Vergnaud JM, Rollet M. (1994). Modelling of release kinetics of drugs from irradiated NaCMC matrix. Int J Pharm, 110:285–289.
25. Williams RO 3rd, Reynolds TD, Cabelka TD, Sykora MA, Mahaguna V. (2002). Investigation of excipient type and level on drug release from controlled release tablets containing HPMC. Pharm Dev Technol, 7:181–193.
26. Samani SM, Montaseri H, Kazemi A. (2003). The effect of polymer blends on release profiles of diclofenac sodium from matrices. Eur J Pharm Biopharm, 55:351–355.
27. Salsa T, Veiga F, Teixeira-Dias JJ, Pina ME. (2003). Effect of polymer hydration on the kinetic release of drugs: a study of ibuprofen and ketoprofen in HPMC matrices. Drug Dev Ind Pharm, 29:289–297.
28. Ritger PL, Peppas NA. (1987). A simple equation for the description of solute release II. Fickian and anomalous release from swellable devices. J Contr Rel, 5:37–42.
29. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. (1983). Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm, 15:25–35.
30. Boateng JS, Auffret AD, Matthews KH, Humphrey MJ, Stevens HN, Eccleston GM. (2010). Characterisation of freeze-dried wafers and solvent evaporated films as potential drug delivery systems to mucosal surfaces. Int J Pharm, 389:24–31.
31. Corrigan OI, Stanley CT. (1982). Mechanism of drug dissolution rate enhancement from beta-cyclodextrin-drug systems. J Pharm Pharmacol, 34:621–626.
32. Peppas NA. (1985). Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv, 60:110–111.
33. Rinaki E, Valsami G, Macheras P. (2003). The power law can describe the 'entire' drug release curve from HPMC-based matrix tablets: a hypothesis. Int J Pharm, 255:199–207.
34. Ayensu I, Mitchell JC, Boateng JS. (2010). Freeze dried thiolated chitosan formulations for protein delivery via the buccal mucosa. J Pharm Pharmacol, 62:S1273.
35. Kianfar F, Chowdhry BZ, Antonijevic MD, Boateng JS. (2010). Design and formulation of a novel polymer based buccal film. J Pharm Pharmacol, 62:S1259.
36. Rai D, Maniruzzaman M, Boateng JS. (2010). Development and characterisation of sodium alginate and HPMC films for mucosal drug delivery. Int J Biotechnology, 11:169–181.