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In vitro drug release studies of polymeric freeze-dried wafers and solvent-cast films using paracetamol as a model soluble drug

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ABSTRACT

Drug dissolution and release characteristics from freeze-dried wafers and solvent-cast films prepared from sodium carboxymethylcellulose (CMC) have been investigated to determine the mechanisms of drug release from the two systems. The formulations were prepared by freeze-drying (wafers) or drying in air (films), the hydrated gel of the polymer containing paracetamol as a model soluble drug. Scanning electron microscopy (SEM) was used to examine differences between the physical structure of the wafers and films. Dissolution studies were performed using an exchange cell and drug release was measured by UV spectroscopy at 242 nm. The effects of drug loading, polymer content and amount of glycerol (films) on the release characteristics of paracetamol were investigated. The release profiles of paracetamol from the wafers and films were also compared. A digital camera was used to observe the times to complete hydration and dissolution of the wafers containing different amounts of CMC and how that impacts on drug release rates. Both formulations showed sustained type drug release that was modelled by the Korsmeyer–Peppas equation. Changes in the concentration of drug and glycerol (films) did not significantly alter the rate of drug release while increasing polymer content significantly decreased the rate of drug release from both formulations. The results show that the rate of paracetamol release was faster from the wafers than the corresponding films due to differences in their physical structures. The wafers which formed a porous network, hydrated faster than the more dense and continuous, (non-porous) sheet-like structure of the films.

1. Introduction

The study of drug release from polymeric systems such as sodium carboxymethylcellulose (CMC) is important in the formulation of pharmaceutical dosage forms (Paavola et al., 1998). Drug release from such systems usually involves the uptake of water by the glassy polymer and subsequent swelling to form a gel layer, which controls drug release by viscous resistance to drug diffusion. The diffusion of a water-soluble drug through the gel layer has classically been shown to be linearly dependent on the square root of time. However, swellable polymer systems also exhibit erosion, which introduces another release mechanism to be accounted for (Korsmeyer et al., 1983). Several equations have been proposed that attempt to accommodate a dual release mechanism (i.e. drug diffusion through the gel and erosion of the gel layer). The most common of these is the Peppas transport equation (Ritger and Peppas, 1987) which has been employed to describe the initial 60% of drug release. The magnitude of '*n*' in the Peppas equation (Eq. (1)) can be used as an indication of diffusion controlled drug release.

CMC is non-ionic cellulose ether commonly used in controlled release hydrophilic matrix systems. It is non-toxic and has the ability to accommodate high drug loadings (Podczeck et al., 2008). CMC is also a known good film former and a key component of hydrocolloid wound dressings. Formulations comprising CMC or other hydrophilic polymers such as HPMC and xanthan have great potential for delivery of drugs to moist surfaces such as nasal cavity (Ugwoke et al., 2000; McInnes et al., 2007) and wounds (Matthews et al., 2005, 2006). This is possible due to their bioadhesive nature, ease of hydration and subsequent swelling to form a gel which controls drug release (Ludwig, 2005; Boateng et al., 2008).

This paper describes the dissolution properties of freeze-dried wafers and solvent evaporated films prepared from CMC, containing varying amounts of drug, polymer, and glycerol (films).

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Paracetamol was chosen as a model soluble drug (class I) according to the biopharmaceutics classification system (Amidon et al., 1995). The release characteristics of paracetamol from the wafers and films were compared to investigate the effects of differences in their physical structure determined by scanning electron microscopy (SEM) on the release profiles. The drug release data were fitted to the Korsmeyer–Peppas equation, zero-order, first-order and Higuchian equations to identify the equation that best models release of paracetamol from the wafers and films. The effect of different variables (amounts of polymer, drug and glycerol) and formulation type (wafer and film) on drug release characteristics were also investigated. These help to understand the relationship between drug release characteristics and the two different formulations (wafers and films) prepared from CMC polymer.

2. Materials and methods

2.1. Materials

Sodium carboxymethylcellulose—CMC (Blanose 7H4XF Food Grade) was obtained from Hercules, USA. Paracetamol and glycerol were all purchased from Sigma (Gillingham, UK).

2.2. Preparation of wafers and films

Three distinct formulations (both wafers and films) were prepared to investigate the effects of (a) paracetamol (b) CMC and (c) glycerol contents on the drug release characteristics of the wafers and films. Glycerol in the films (two out of the three formulations) was used as a plasticizer. The actual compositions and the specific amounts of paracetamol, CMC and glycerol in each formulation are summarised in Table 1. The gels for preparing the wafers and unplasticised films (no glycerol) were obtained by first dissolving the paracetamol in hot distilled water (90 °C and the CMC powder dispersed into the vortex of the vigorously stirred hot paracetamol solution. For plasticised films, the correct amount of glycerol was first added to the paracetamol solution before the CMC was dispersed into the vortex of the hot solution. Each wafer and film was prepared by pouring 5 g of the different gels into separate containers all having the same diameter and allowed to cool. The gels were then freeze-dried (wafers) or dried in an oven at 45 °C and 6% relative humidity (films) (Boateng et al., 2009).

2.3. Scanning electron microscopy (SEM)

SEM images of gold-coated wafers and films were obtained using a Phillips SEM 515, with a spot size of 320 Å and 12 kV intensity at a magnification of 100.

2.4. Hydration and dissolution of wafers

Hydration and subsequent dissolution of wafers prepared from different CMC solutions (0.5–3.0%, w/w) were investigated in a diffusion apparatus (McInnes et al., 2005). The wafers were placed on a stainless steel wire mesh in the donor compartment and just wetted on the underside by contact with distilled water in the receiver compartment. This allowed the hydration to be observed in one direction beginning from the side of the wafer in direct contact with the water. An RDC50 digital camera, equipped with a 2.3 M pixel supa-macro zoom facility, was positioned to face the hydrating freeze-dried wafer in the assembled device at a distance of 5 cm. The camera was programmed to acquire

Table 1
Composition of the wafers and films for investigating effect of paracetamol, CMC and glycerol (films) content on drug release characteristics. Formulations labelled as (Ref) were those selected as references for comparing the release curves of the different formulations c.f. tablet 5.

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

Content of paracetamol of total dry weight (%, w/w)	Weight of paracetamol per wafer and film (mg)	Weight of CMC per wafer and film (mg)	Weight of glycerol per film (mg)
0.3	0.3	100	–
0.5	0.5	100	–
1.0	1.0	100	–
1.5	1.5	100	–
2.0	2.0	100	–
2.4	2.5	100	–
9.1	10.0	100	–
16.7 (Ref)	20.0	100	–
23.1	30.0	100	–
33.3	50.0	100	–
41.2	70.0	100	–
47.4	90.0	100	–

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

CMC content of solution used (%, w/w)	Weight of paracetamol 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 paracetamol

Ratio of GLY:CMC (by weight)	Weight of paracetamol per film (mg)	Weight of CMC per film (mg)	Weight of glycerol per film (mg)
0:1 (Ref)	20	100	0
1:1	20	100	100
3:2	20	100	150
2:1	20	100	200

images at 2–10 min intervals until the formulations completely disappeared by dissolution. The time to complete hydration and total dissolution of the wafers were noted.

2.5. In vitro drug release studies

Before the drug release experiments, absorbance values of seven calibration solutions (0–2 mg/100 mL) were measured at 242 nm with a Thermospectronic UV Spectrophotometer (Helios Alpha, England, UK). The specific absorbance was calculated from the slope of a standard calibration curve, obtained by plotting the concentration of the solutions against absorbance (Fig. 2). To ensure that none of the other ingredients (CMC and glycerol) did not affect the UV absorption, a 0.5% (w/w) solution of CMC and glycerol was scanned between 200 and 600 nm which yielded a flat spectrum with no absorption near the absorption maxima of paracetamol (242 nm).

The *in vitro* dissolution and release properties of paracetamol in wafers and films were investigated with the diffusion apparatus used for the hydration experiment above, containing 125 mL of distilled water at 37 °C. At given intervals, 5 mL of solution was sampled and replaced with fresh distilled water also maintained at 37 °C. Where necessary, the sampled solution was diluted with distilled water to fall within the range of the UV standard calibration curve. The drug released was measured by UV spectroscopy at a wavelength of 242 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.

2.6. Drug release kinetics

The kinetics of paracetamol release from the wafers and films was determined by finding the best fit of the curves (% release against time) to distinct models (Eqs. (1)–(4)).

$$\ell_n\left(\frac{Q_t}{Q_\infty}\right) = \ell_n k + n\ell_n t \quad \text{(Korsmeyer–Peppas)} \tag{1}$$

Q_t is the amount of drug released at a given time (t), Q_∞ is the amount of drug present initially, k is a constant comprising the structural and geometric characteristics of the formulation and n is the release exponent.

$$Q_t = k_H t^{1/2} \quad \text{(Higuchi Equation)} \tag{2}$$

Q_t is the amount of drug released at time (t), k_H is the Higuchian release rate constant.

$$Q_t - Q_0 = k_0 t \quad \text{(Zero order equation)} \tag{3}$$

Q_t the amount of drug released in time (t), Q_0 is the amount of drug dissolved at time zero, k_0 is the zero-order release constant.

$$\ell_n\left(\frac{Q_\infty}{Q1}\right) = k_1 t \quad \text{(First order equation)} \tag{4}$$

Q_1 is the amount of drug remaining at time (t), Q_∞ is the total amount of drug present initially, k_1 is the first-order rate constant.

2.7. Comparison of release profiles

The drug release characteristics for the two formulations (wafers and films) and variables (drug, CMC and glycerol concentrations) under investigation were compared, by calculating the difference (f_1) and similarity (f_2) factors (Yuksel et al., 2000; Rinaki et al., 2003). The f_1 value (Eq. (5)) measures the percent error between two curves over all time points, while the f_2 value (Eq. (6)) is a logarithmic transformation of the sum-squared error of differences between the test T_j and reference products R_j over all time points.

$$f_1 = \frac{\sum_{j=1}^{n}|R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100 \tag{5}$$

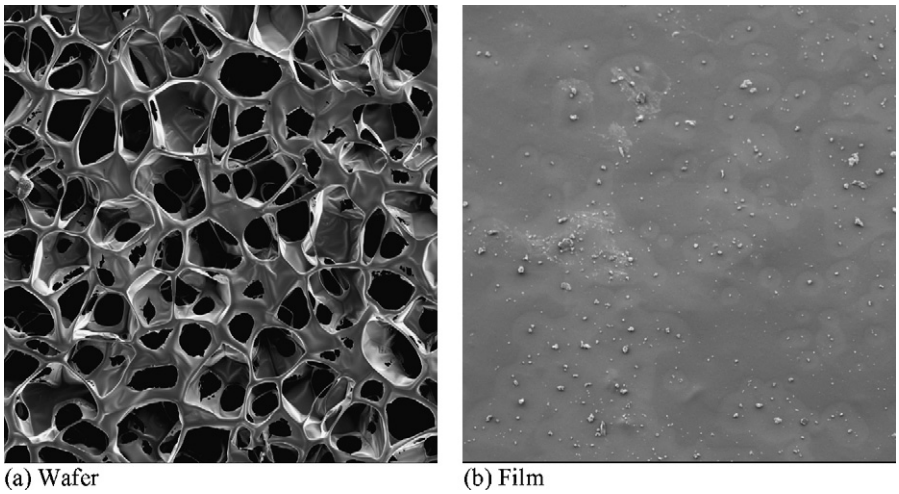
$$f_2 = 50 \times \log\left\{\left(1 + (1/n)\sum_{j=1}^{n} W_j|R_j - T_j|^2\right)^{-0.5}\right\} \times 100 \tag{6}$$

Release curves are considered similar when the calculated f_1 value is close to 0 and f_2 is 50–100 respectively (FDA guidance document, 1997; EMEA guidance document, 2001). The formulation selected from the different type of wafers and films as references for the purposes of comparing the release curves are highlighted in parenthesis as 'Ref' in Table 1.

3. Results

3.1. Scanning electron microscopy

The SEM images showed differences between the physical structure of the freeze-dried wafers and solvent-cast films. The wafers



(a) Wafer (b) Film

Fig. 1. Typical SEM images of paracetamol containing (a) freeze-dried wafer and (b) solvent-cast film prepared from 2% (w/w) CMC solution. The difference in the physical microstructure between the porous wafers and non-porous films is clearly evident.

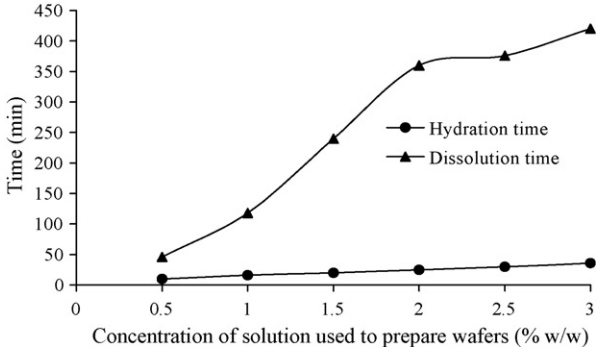


Fig. 2. Effect of polymer content (%, w/w) on the hydration and dissolution times of CMC wafers.

formed a porous interconnecting network while the corresponding films formed a dense continuous (non-porous) sheet (Fig. 1).

3.2. Hydration and dissolution of wafers

The result of the hydration study of the wafers is summarised with Fig. 2 indicating an increase in the time taken for complete hydration and dissolution with increasing CMC content. The purpose of this study was to mimic the swelling and dissolution behaviour of the wafers during drug release studies as they influence the drug release characteristics.

3.3. Release of paracetamol from wafers

The standard calibration curve of paracetamol in distilled water is shown in Fig. 3 and proves that Beer's law was maintained. The percentage cumulative release profiles of paracetamol from CMC wafers at different levels of drug concentration are shown in Fig. 4a. Wafers containing 16.7% (w/w) of paracetamol produced the fastest release rate, releasing 50% of the initial amount of paracetamol present by 61 min while those containing 33% (w/w) paracetamol showed the slowest release profile with t_{50} of 122 min. The change in release profiles of paracetamol in wafers containing increasing concentration of CMC is shown in Fig. 4b. The release rates of paracetamol from these wafers, obtained from the linear portions (first 60% of release) of the dissolution curves are summarised in Table 2.

3.4. Release of paracetamol from films

Fig. 5a shows the release profiles of CMC films containing different amounts of paracetamol. Films containing 16.7% (w/w) of

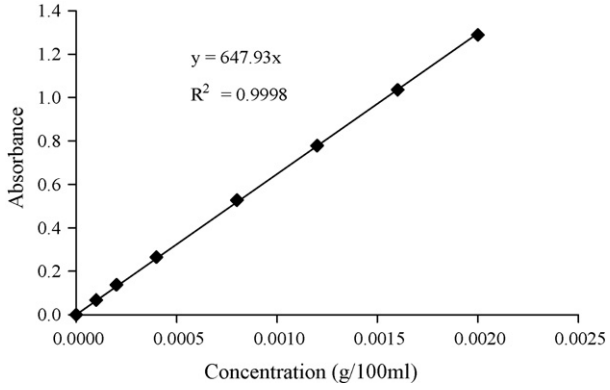


Fig. 3. Standard UV calibration curve for paracetamol used for determining the release of paracetamol during drug release studies.

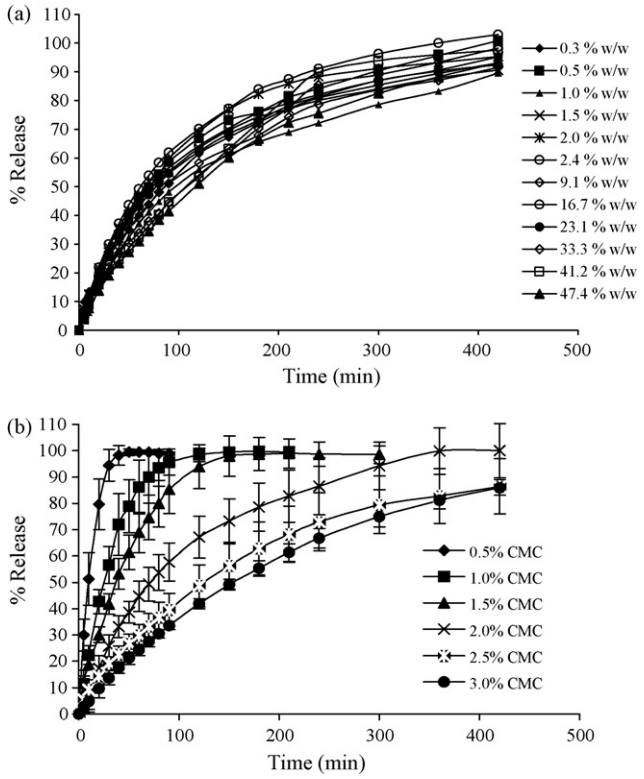


Fig. 4. (a) Percent cumulative drug release from CMC wafers (2%, w/w solution) containing increasing concentrations of paracetamol and (b) effect of increasing polymer concentration on drug release profiles from CMC containing 1% (w/w) of paracetamol (of total dry weight of each formulation), (37 °C, $n = 6$).

paracetamol released the drug fastest as occurred in wafers, while those containing 0.3% (w/w) paracetamol released the drug slowest. The paracetamol release profiles of films containing varying amounts of CMC are shown in Fig. 5b. The release rates of paracetamol from the films, estimated from the linear portions of the curves are shown in Table 2. Fig. 6 shows the drug dissolution profiles from CMC films prepared from 2% (w/w) solutions containing approximately 1 mg of paracetamol and varying amounts of glycerol.

3.5. Kinetic mechanism and comparison of release profiles

Representative plots obtained by fitting experimental release data to four kinetic models are shown in Fig. 7. The rest of the data are summarised in Tables 3 and 4 using the Peppas power equation which best modelled the release data while the f_1 and f_2 values for the various formulations are summarised in Table 5. Paracetamol release rate was generally faster from the wafers than their corresponding films.

Table 2
Effect of polymer content on the release rate (%/min) of paracetamol (1%, w/w) from CMC wafers and plasticised films estimated from the linear portion of the dissolution curves ($n = 6$), c.f. Figs. 4b and 5b.

CMC content (%, w/w)	Mean rate of release (%/min) (±s.d.)	
	Wafers	Films
0.5	3.9 (0.7)	2.5 (0.3)
1.0	1.7 (0.2)	1.5 (0.2)
1.5	1.0 (0.2)	0.9 (0.1)
2.0	0.5 (0.1)	0.7 (0.1)
2.5	0.4 (0.1)	0.5 (0.1)
3.0	0.4 (0.0)	0.4 (0.1)

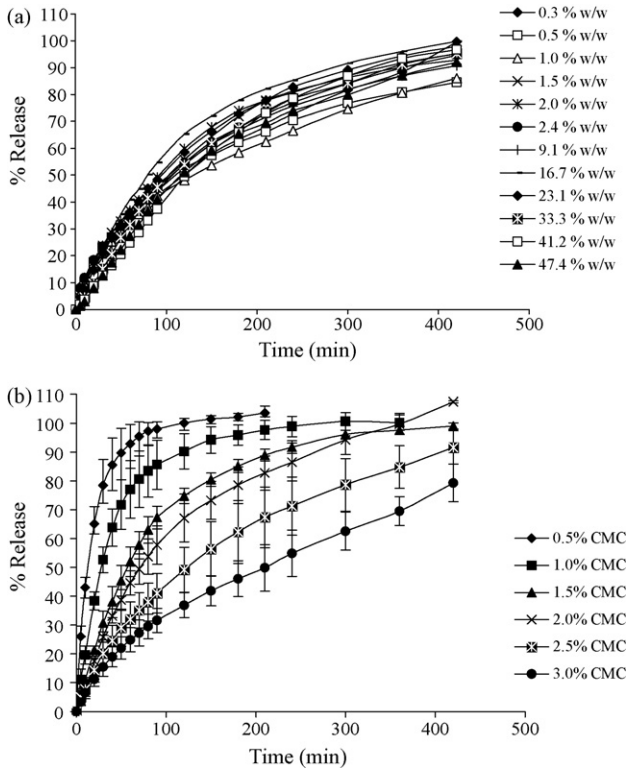


Fig. 5. (a) Effect of drug loading on release profile of paracetamol from unplasticised CMC films (2%, w/w solution) and (b) effect of CMC content on the drug release profiles from plasticised (100 mg glycerol per film) CMC films containing 1% (w/w) of paracetamol (37 °C, $n = 6$).

4. Discussion

The wafers and films consisted of a simple blend of CMC and paracetamol. Films for investigating the effects of polymer content also contained glycerol as plasticizer. This was because unplasticised films (no glycerol) prepared from 0.5 to 1.0% (w/w) solutions were too thin for easy removal without any damage while those prepared from 2.5 to 3.0% (w/w) solutions were too brittle and deformed or cracked. The addition of glycerol yielded more flexible films with increased thickness, therefore rendering them easier to remove (Boateng et al., 2009).

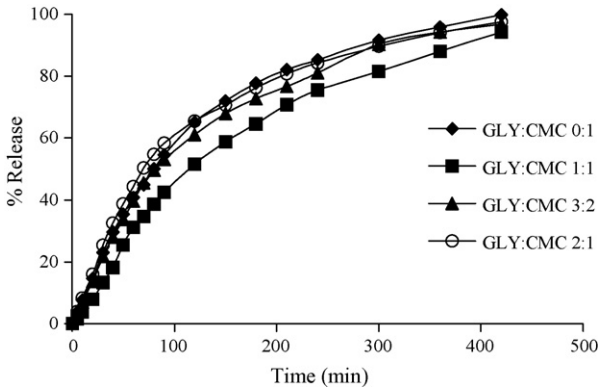


Fig. 6. Drug release profiles of CMC films containing increasing amounts of glycerol and fixed content of paracetamol (16.7%, w/w).

Dissolution studies of paracetamol containing CMC wafers and films generally yielded sustained release profiles. The drug concentration in both wafers and films had no significant effect on the release profiles, rates of release and the mechanism of release. This was shown by the similarity (f_1) and difference (f_2) factors, which confirmed that the release profiles for these formulations were all similar. The result implies that factors other than drug solubility and mass transfer (diffusion) phenomena were involved. The two important factors suggested for this study were hydration and swelling properties of the formulations, which depended largely on the amount of polymer present as seen from the results of the wafer hydration experiment.

The decrease in drug release rate with increase polymer content (Table 2) can be attributed to resultant increase in the mechani-

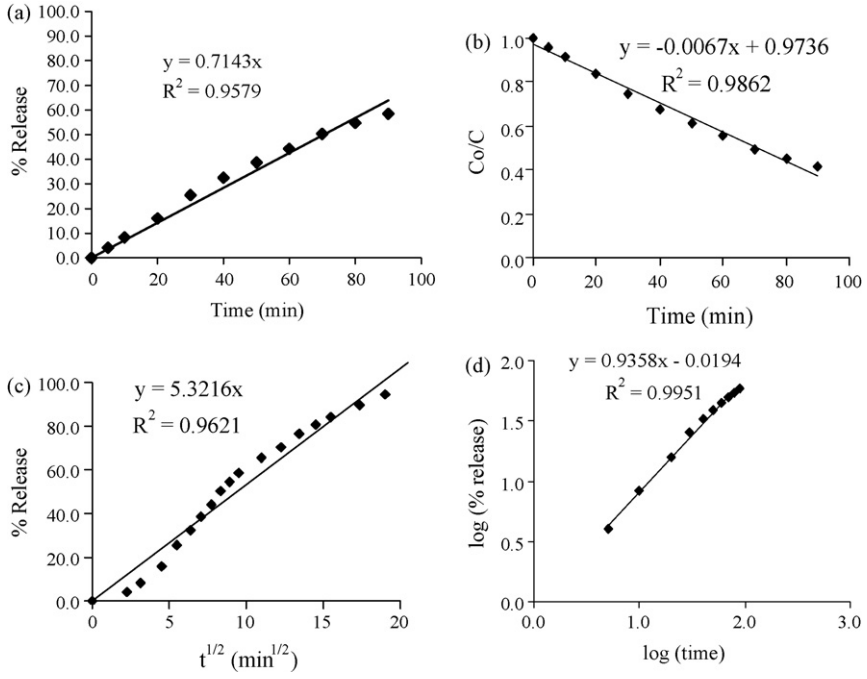


Fig. 7. Representative release plots obtained by fitting experimental release data of paracetamol from CMC wafers and films to (a) zero-order, (b) first-order, (c) Higuchi and (d) Korsmeyer–Peppas kinetic equations.

Table 3
Results obtained by fitting the experimental drug release data to the Korsemeyer–Peppas kinetic equation for CMC wafers and films (2%, w/w) containing different amounts of paracetamol (0.3–47.4%, w/w). K_p values are mean release rates (% min^{-n}) of 6 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.

Paracetamol content (%, w/w)	Wafers			Films		
	K_P (% min^{-n}) (±s.d.)	n	r^2	K_P (% min^{-n}) (±s.d.)	n	r^2
0.3	3.7 (±1.0)	0.5	0.996	3.9 (±1.0)	0. 6	0.996
0.5	1.9 (±0.5)	0.9	0.997	2.5 (±0.3)	0.7	0.995
1.0	2.5 (±0.8)	1.1	0.962	2.4 (±0.7)	0.6	0.998
1.5	2.6 (±0.4)	0.7	0.996	1.6 (±0.4)	0.8	0.995
2.0	3.0 (±0.9)	0.7	0.998	1.9 (±0.4)	0.7	0.997
2.4	2.1 (±0.7)	0.7	0.996	2.9 (±0.2)	0.6	0.999
9.1	1.5 (±0.4)	0.8	0.987	1.5 (±0.1)	0.8	0.999
16.7	1.7 (±0.2)	0.8	0.993	1.0 (±0.2)	0.9	0.995
23.1	2.0 (±0.3)	0.7	0.991	0.9 (±0.2)	0.9	0.993
33.3	1.7 (±0.2)	0.7	0.993	0.5 (±0.2)	1.0	0.993
41.2	1.3 (±0.3)	0.8	0.991	0.4 (±0.1)	1.0	0.998
47.4	1.2 (±0.2)	0.8	0.996	0.4 (±0.2)	1.2	0.992

Table 4
Results obtained by fitting the experimental drug release data to the Korsmeyer–Peppas kinetic equation for CMC wafers and plasticised films (0.5–3.0%, w/w of CMC) containing 1 mg of paracetamol. K_p values are mean release rates (% min^{-n}) of 6 replicate samples, r^2 is the correlation coefficient, n is the release exponent.

Polymer content (%, w/w)	Wafers			Films		
	K_P (% min^{-n}) (±s.d.)	n	r^2	K_P (% min^{-n}) (±s.d.)	n	r^2
0.5	10.1 (±1.7)	0.7	0.997	9.3 (±1.1)	0.7	0.985
1.0	4.3 (±0.1)	0.9	0.997	3.8 (±1.0)	0.9	0.992
1.5	3.4 (±0.8)	0.7	0.999	1.6 (±0.4)	0. 9	0.993
2.0	2.6 (±0.5)	0.9	0.990	1.2 (±0.3)	0.9	0.986
2.5	1.9 (±0.4)	0.7	0.999	1.1 (±0.7)	0.7	0.987
3.0	1.7 (±0.2)	0.9	0.997	1.0 (±0.3)	0.7	0.988

cal strength of these formulations which determines their rate of hydration and eventual dissolution. This ultimately affects the rate at which the drug diffused through the gel and was released into the dissolution medium. It has been reported that the rate and extent of drug release, as well as the mechanism of drug release are affected by the type and amount of polymer (Williams et al., 2002), the proportion and grade of polymer (Samani et al., 2003) and polymer hydration characteristics (Salsa et al., 2003). Changing release profiles with varying amounts of CMC were observed for the wafers (Fig. 4b). Wafers prepared from 0.5 to 1.5% (w/w) CMC solutions released their content of drug relatively faster due to more rapid hydration and disintegration (dissolution) with swelling phase lasting only for a short period of time. The wafers containing higher amounts of CMC (2.0–3%, w/w) hydrated and swelled more slowly to produce a gel, which slowly disintegrated, resulting in sustained release profiles. Similar observations were made for the films (Fig. 5b) though not to the same extent because release from wafers and films varied.

The formulations for investigating the effect of paracetamol content all contained the same proportion of CMC by weight. They

Table 5
Similarity and difference factors for comparing release curves with respect to drug loading, CMC and glycerol content (films) effect on release profiles relative to the reference (Ref) formulations.

Variable Components	Variable (%, w/w)	Similarity factor (f_1)		Difference factor (f_2)	
		Wafers	Film	Wafers	Film
Paracetamol content	0.3	13.9	14.5	53.1	52.1
	0.5	6.7	5.5	67.7	71.5
	1.0	19.8	6.9	45.1	67.6
	1.5	11.2	9.2	56.1	62.8
	2.0	4.1	7.2	74.6	68.6
	2.4	9.5	11.9	60.0	58.1
	9.1	16.5	13.7	49.2	54.7
	16.7	Ref	Ref	Ref	Ref
	23.1	10.8	6.3	57.5	70.1
	33.3	16.9	13.8	47.4	55.5
	41.2	16.4	18.8	47.4	47.5
	47.4	23.3	20.1	41.8	47.7
CMC content	0.5	200.4	90.1	37.5	20.4
	1.0	93.9	44.1	21.5	32.8
	1.5	43.9	12.3	32.9	60.2
	2.0	Ref	Ref	Ref	Ref
	2.5	8.6	25.4	64.5	44.4
	3.0	19.1	45.9	50.0	31.4
Glycerol content (GLY:CMC)	0:1	–	Ref	–	Ref
	1:1	–	17.7	–	50.3
	3:2	–	4.0	–	77.5
	2:1	–	4.0	–	78.1

therefore produced similar sustained release profiles as a result of the viscous gel formed after initial hydration (Figs. 4a and 5a). Gel erosion also played an important role owing to the water solubility of sodium CMC which allowed 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 (Ritger and Peppas, 1987). 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 (Korsmeyer et al., 1983).

The release of paracetamol was generally faster from the wafers than from the corresponding films, which was particularly true at the initial 60% of release. These differences in release rate could be attributed to the differences between the physical properties of the wafers and films, which affected their initial rate of hydration and swelling. The wafers which were porous in nature, allowed a faster rate of water ingress than the dense and continuous films (Fig. 1). Therefore the rate of swelling, dissolution and subsequent diffusion of paracetamol from the resulting gel was faster from the wafers than the films.

Fitting of the dissolution data to the four kinetic models and investigation of the r^2 values showed that the Kormeyer–Peppas equation modelled the release curves most accurately. Drug release from swellable matrices is usually complex and though some processes may be distinctly classified as either diffusion or erosion controlled, drug release is mostly governed by both 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. Over all, the release exponents generally varied from 0.5 to 1.2 for all the formulations. These values of n show an anomalous (non-Fickian) transport for most of the formulations, suggesting that both diffusion of paracetamol through the hydrated polymer combined with gel erosion controlled drug release. In addition, the different formulation variables investigated (drug, polymer and glycerol content) did not alter the mechanism of paracetamol release from CMC wafers and films.

5. Conclusions

The release characteristics of paracetamol from the CMC wafers and films followed a sustained type release profile determined largely by matrix swelling and drug diffusion through the swollen matrix. The rate of drug release from the wafers (porous) and films (non-porous) was dependent on their physical structure and the amount of polymer present. These differences present the possibility of using these formulations in different mucosal applications. The wafers which can absorb moisture at a faster rate will be useful for applying onto and delivering active agents to suppurating wounds. The faster release rate of drug from wafers and films containing low polymer levels also make them suitable as drug delivery systems such as fast dissolving tablets and films for buccal administration of drugs. Wafers and films containing higher amounts of the polymer which hydrate at a slower rate will potentially be better suited for controlled release applications both in the buccal cavity and on wound surfaces.

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