Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmaceutics and Biopharmaceutics 57 (2004) 541–549
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

The effect of wet granulation on the erosion behaviour of an HPMC–lactose tablet, used as a rate-controlling component in a pulsatile drug delivery capsule formulation

Jason T. McConville[a,*], Alistair C. Ross[a], Alan R. Chambers[a], Geoff Smith[b], Alastair J. Florence[a], Howard N.E. Stevens[a]

[a]*Department of Pharmaceutical Sciences, University of Strathclyde, Glasgow, UK*
[b]*School of Pharmacy and Pharmaceutical Sciences, De Montfort University, Leicester, UK*

Received 22 October 2003; accepted in revised form 20 January 2004

Abstract

The purpose of this study was to investigate the variability in the performance of a pulsatile capsule delivery system induced by wet granulation of an erodible HPMC tablet, used to seal the contents within an insoluble capsule body. Erodible tablets containing HPMC and lactose were prepared by direct compression (DC) and wet granulation (WG) techniques and used to seal the model drug propranolol inside an insoluble capsule body. Dissolution testing of capsules was performed. Physical characterisation of the tablets and powder blends used to form the tablets was undertaken using a range of experimental techniques. The wet granulations were also examined using the novel technique of microwave dielectric analysis (MDA). WG tablets eroded slower and produced longer lag-times than those prepared by DC, the greatest difference was observed with low concentrations of HPMC. No anomalous physical characteristics were detected with either the tablets or powder blends. MDA indicated water-dipole relaxation times of 2.9, 5.4 and 7.7×10^{-8} ms for 15, 24 and 30% HPMC concentrations, respectively, confirming that less free water was available for chain disentanglement at high concentrations. In conclusion, at low HPMC concentrations water mobility is at its greatest during the granulation process, such formulations are therefore more sensitive to processing techniques. Microwave dielectric analysis can be used to predict the degree of polymer spreading in an aqueous system, by determination of the water-dipole relaxation time.
© 2004 Published by Elsevier B.V.

Keywords: Pulsatile delivery; Lag-time; Microwave dielectric analysis; HPMC; Erosion; High shear granulation

1. Introduction

Time-delayed dosage forms permit the delivery of drugs after a pre-determined lag-time [1] and this can have clinical significance where a disease state has shown circadian rhythm dependency [2]. For example, there are morning peaks in the onset of myocardial infarction, sudden death and stable angina in coronary heart disease patients [3]; provision of a suitable medication, such as verapamil [4], at the right time could potentially alleviate these conditions.

A pulsed-release capsule delivery device has been developed by this group where the release time can be controlled by varying the properties of an erodible tablet used to seal a drug inside an impermeable capsule body (Fig. 1).

Ross et al. determined that although hydrophobic excipients could be used in conjunction with lactose to control the tablet erosion rate [5], such formulations were susceptible to incidence of failure resulting in premature drug expulsion [6]. An alternative approach was to use HPMC and lactose combinations to form an erodible hydrophilic gel matrix system. Such compositions have previously been used successfully to produce controlled release preparations and their mode of action to produce sustained release is well documented [7]. Capsule-based systems using this type of polymer-based erodible tablet have demonstrated their potential with an array of designs [8]. It has also been determined by this group that directly compressed

* Corresponding author. Present address: College of Pharmacy, University of Texas at Austin, 1 University Station A1920, Austin, TX 78712-0126, USA. Tel.: +1-512-232-5188; fax: +1-512-471-7474.
E-mail address: jtmcconville@mail.utexas.edu (J.T. McConville).

0939-6411/$ - see front matter © 2004 Published by Elsevier B.V.
doi:10.1016/j.ejpb.2004.01.004

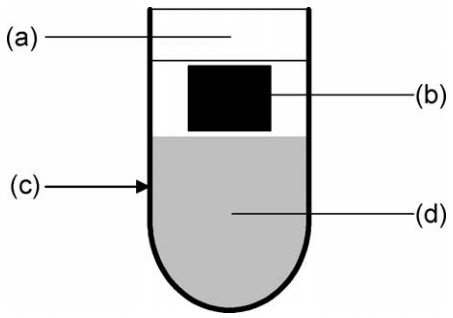

Fig. 1. Assembled pulsed release capsule device. (a) Erodible tablet; (b) propranolol tablet; (c) insoluble ethyl cellulose coated capsule body; (d) low-substitued hydroxypropyl cellulose expulsion excipient. Tablet (a) is positioned using a flat edged metallic block ensuring it is flush with the top of the capsule body.

HPMC/lactose combinations could be used to produce erodible tablets capable of affording a range of time-delays from the assembled capsule device. It was noted that the tablets provided a degree of swelling on contact with water at the open end of the capsule, ensuring a good seal, and preventing premature drug release.

In an attempt to reduce the observed variability in lag-time, a wet granulation step was introduced in order to improve the homogeneity of the powder blends prior to tableting. Significant reductions in tablet dissolution variability have previously been demonstrated by introduction of a wet granulation step [9]. In addition, previous reports using high molecular weight Methocel® [10], found no difference between direct compression and wet granulation formulations when comparing controlled drug release rates. However, in the studies we now report, wet granulation has been found to significantly alter the erosion properties of HPMC/lactose tablets and led to prolongation of the lag-times from the time-delayed capsule formulation.

2. Materials and methods

Hydroxypropylmethyl cellulose (Methocel®, K100LV grade) and ethylcellulose were obtained from the Dow Chemical Company, Midland, MI, USA. Low-substituted hydroxypropyl cellulose (L-HPC®, LH-21 grade) was obtained from Shin-Etsu Chemical Company, Tokyo, Japan. Propranolol hydrochloride and all tablet excipients (magnesium stearate, Aerosil R728 and Fast-flo lactose) were obtained as gifts from Pfizer Central Research, Sandwich, UK. Size 0 gelatin capsules (Capsugel, Greenwood, SC, USA) were also obtained from Pfizer. BW-Manesty Ltd, Liverpool, UK, supplied size 0 gelatin capsules, pre-coated with ethyl cellulose (Ethocel®, 45 premium grade). The capsule coating method employed identical conditions to those previously described [5].

2.1. Manufacture of direct compression erodible tablets

Direct compression erodible tablet formulations containing 15, 24 and 30% HPMC were prepared by weighing 15, 24 and 30 g of HPMC and adding lactose to 99 g. Each formulation was mixed in a Turbula™ mixer (Glen Creston, Stanmore, UK) for 25 min at 42 rev./min. Magnesium stearate (1 g) was added to each blend and further mixed (5 min). The resultant blends were tableted to 80 ± 2 mg using 6.75 mm flat-faced punches using a single punch E2 tablet press (BW-Manesty, Liverpool, UK).

2.2. Manufacture of wet granulation erodible tablets

Wet granulated erodible tablet formulations containing 15, 24 and 30% HPMC were prepared with 15, 24 and 30 g HPMC and lactose (to 99 g) by mixing using an FP296 mixer/granulator (Kenwood Ltd, Watford, UK). Water (25 ml) was added slowly using a pasteur pipette at a mixing speed of 1350 rev./min. The resultant granules were spread evenly on a tray and dried overnight (50 °C). The granules were passed through a 300 μm sieve and 49.5 g of each was taken and dry blended in the Turbula™ mixer with magnesium stearate (0.5 g) for 5 min. The final blends were tableted as above.

2.3. Manufacture of model propranolol tablets

The capsule contents were in the form of a tablet formed from a powder blend of propranolol hydrochloride (51 g), lactose (48 g) and Aerosil® (0.1 g) which was mixed in the Turbula™ for 25 min before adding 1 g magnesium stearate followed by further mixing (5 min). The mixture was then tableted to 80 ± 2 mg using 5 mm flat-faced punches as above. Tablets were used in this study to bulk prepare the model drug, it is also possible to fill the drug containing layer of the capsule with granules which may subsequently be expelled by the expanding L-HPC layer on contact with water (Fig. 1). Formulating the drug layer in either a tablet or granule form allows water to percolate through to the expulsion layer prior to solubilisation of the drug. However, previous work has shown that if unprocessed drug powder were used in the active layer of the capsule device then rapid expulsion does not occur before significant drug solubilisation, this subsequently leads to entrapment of the drug within the expanding L-HPC layer (data not shown).

2.4. Pulsatile capsule assembly

Assembly of the pulsed-release capsule device proceeded as follows: (i) L-HPC (250 mg) was weighed into the pre-coated capsule body and lightly compacted using a 2 N force; (ii) a propranolol tablet was placed onto the compacted L-HPC layer; (iii) an erodible HPMC/lactose tablet was inserted into the mouth of the capsule and positioned flush (by pushing the tablet home with

a flat edged metallic block) with the end of the coated body (Fig. 1).

2.5. Physical characteristics of erodible tablets

Physical testing of weight, crushing strength, thickness and diameter of the erodible tablets prepared by either direct compression or wet granulation was performed using an TBH30 tablet testing station (Erweka GmbH, Heusenstamm, Germany). Percent relative porosity values were calculated using the relationship of apparent density and true density [11]. Apparent density was calculated using the tablet parameters obtained from the testing station, whilst true density was determined using a helium pycnometer (Micromeritics, Norcross, GA, USA).

2.6. Dissolution testing

Dissolution testing was carried out using a USP II paddle apparatus, model ST7 (G.B. Caleva Ltd, Sturminster Newton, UK) at 37 °C in 1000 ml degassed and deionised water and a paddle speed of 50 rev./min. A non-parametric Mann–Whitney test was used to compare individual $T_{50\%}$ drug release time for each formulation type.

2.7. Diffuse reflective infrared fourier transform spectroscopy (DRIFTS)

DRIFTS measurements were collected from samples (10 mg) of the lactose or HPMC pre- and post-granulation with water using an Avatar 360-FTIR (Nicolet Instrument Technologies Inc., Madison, WI, USA).

2.8. X-ray powder diffraction (XRPD)

XRPD data were obtained for both samples of lactose (as above). Each sample was filled into a 0.7 mm borosilicate glass capillary tube. The capillary was mounted and aligned on a Bruker-AXS D8 Advance X-ray diffractometer (Brüker Instruments, Karlsruhe, Germany). Data were collected using primary monochromated radiation (Cu $K\alpha_{1-}$, $\lambda = 1.54056$ Å), a position sensitive detector, 0.0145° 2θ step size and a count time of 2.0 s per step.

2.9. Rheological analysis

For rheological analysis, solutions containing 2% HPMC were prepared using 100 ml deionised water at 20 °C using each of the direct compression and wet granulation powder samples. Using a CSL100 rheometer (Carrimed Ltd, Surrey, UK) fitted with a cone/plate arrangement with 4 cm diameter and 59 μm truncation, and a 2° cone angle, 0.2 ml of each sample was analysed. Shear stress against shear rate and viscosity against time plots were obtained for each solution.

2.10. Scanning electron microscopy (SEM)

Samples of direct compression dry powder blends and wet processed granules containing 15, 24 and 30% HPMC were examined using scanning electron microscopy (SEM). Samples were mounted on a 1 cm cylindrical metallic stub using double-sided copper tape and excess powder was removed by shaking. Samples were gold coated using a Polaron SC515 sputter coater (Enutech Ltd, Ashford, UK) for 195 s. Two SEM images were obtained using a SEM500 (Philips Ltd, Eindhoven, ND) at 100× and 400× magnification for each sample.

2.11. Dynamic vapour sorption (DVS)

A DVS2000 dynamic vapour sorption apparatus (Scientific Measurement Systems, Manchester, UK) was set at 25 °C with 10% relative humidity (RH) increments at mass equilibrium. The six formulations: 15, 24, 30% HPMC dry powder blends and dried wet processed granules were analysed using a single sorption–desorption cycle (sorption 0–90% RH; desorption 90–0% RH). In addition, HPMC and lactose (both pre- and post-wet granulation) were analysed as controls.

2.12. Microwave dielectric analysis (MDA)

Microwave dielectric analysis of wet granulation samples was determined by first obtaining a three point calibration of a network analyser (Agilent Technologies, Cheshire, UK), performed using a dipole–dielectric measurement: in air; with a shorting block; and in 25 ml distilled water at 25 °C. After calibration the dielectric probe was blotted dry. HPMC wet granulations of 15, 24 and 30% were prepared as above, with the preparation of wet granulated erodible tablets, then placed in the sample holder ensuring that the granules were consolidated in a reproducible manner. The dielectric probe was then lowered to the flat surface of the granules and the frequency of relaxation of the water dipole was measured.

3. Results and discussion

3.1. Physical properties of erodible tablets

The parameters of weight, thickness, tablet crushing strength, diameter and relative porosity for erodible tablets prepared by either direct compression or wet granulation showed no significant differences. Physical properties were thus ruled out as possible causes of variation between dissolution lag-times of the capsules containing either direct compression or wet granulated erodible tablet formulations having identical compositions.

3.2. Dissolution of pulsatile capsule device

Dissolution profiles of propranolol from capsules sealed with direct compression erodible tablet formulations are shown (Fig. 2a). A higher HPMC concentration results in an increased lag-time. This is due to a greater degree of polymer entanglement [12,13] and increase in gel layer thickness [14], both slowing erosion rate. Dissolution profiles from capsule fitted with the various wet granulated erodible tablets (Fig. 2b) demonstrate an unexpected trend, where lag-times have become prolonged in comparison with corresponding dry-blend formulations. As indicated in Section 3.1 this is not due to tablet variability. It should also be noted that all the capsule formulations showed no signs of premature rupturing, and that the ethyl cellulose (Ethocel® 45 Premium) applied using an organic spray coating technique was sufficient to prevent water ingress through the coated gelatine capsule wall. Previous work has shown that premature water ingress may occur using an aqueous coating system and is not present using the organic coating method [6], used for the capsules in this study.

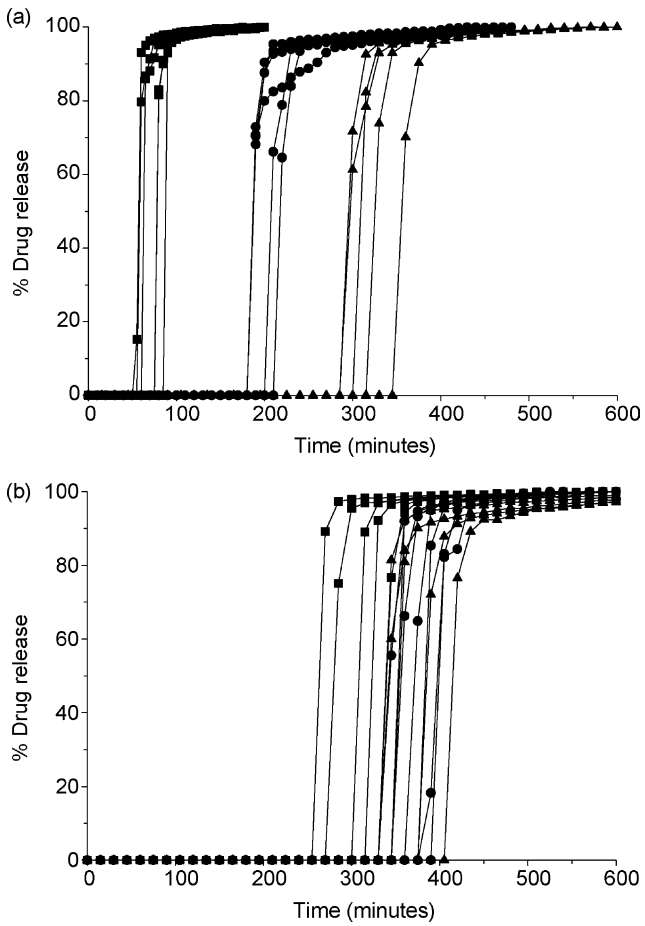

Fig. 2. Release profiles of propranolol from pulsed-release capsules with direct compression erodible tablet formulations: (a) direct compression (DC) blends; (b) wet granulated (WG) blends. ■ 15% HPMC; ● 24% HPMC; ▲ 30% HPMC. ($n = 12$, 6 shown for clarity).

Mean $T_{50\%}$ release times calculated from graphs using a Gompertz sigmoidal equation, indicated that the lag-time variability was not reduced by the wet granulation step. Significant differences between the direct compression and the wet granulated formulations for the 15 and 24% HPMC were observed ($P < 0.05$), but no such difference for the 30% results was seen ($P > 0.05$). The release profiles and the $T_{50\%}$ values suggest that the greatest prolongation of lag-time occurs with the lowest concentration of HPMC (15%), with an observed retardation of 249.1 min. The 24 and 30% formulations indicated lesser, but still show additional lag-times increases of 131.2 and 22.6 min, respectively.

3.3. Diffuse reflectance infrared fourier transform spectroscopy

DRIFTS is a useful technique for the characterisation of molecular solids including amorphous, crystalline and solvated forms. The spectra obtained for the lactose samples (Fig. 3) revealed little difference in the vibrational transitions shown. Absorption due to bound crystalline water is observed at 3524 cm^{-1} [15] and is seen in both pre- and post-granulation lactose; this is consistent with the XRPD analysis (below). This provides no evidence to suggest a change in the physical form of lactose as a result of the granulation process. In addition, no change in the DRIFTS spectra was observed for the HPMC sample post-granulation (data not shown).

3.4. X-ray powder diffraction

The XRPD data are consistent with a largely crystalline sample both pre- and post-granulation. The observed *d*-spacings (data not shown) from both patterns also give good agreement with those calculated from the crystal structure of alpha-lactose monohydrate [16], indicating the lactose is unchanged during the granulation procedure.

3.5. Rheological analysis

Polymer chains may be broken due to the high mechanical stress in the presence of water and has been shown to occur for microcrystalline cellulose using a high shear homogenizer [17]. Although the shear forces involved during this wet granulation procedure are much lower than those found in high shear homogenisation it was deemed necessary to indicate that there was no possibility of HPMC degradation during this process. Had degradation of the HPMC occurred there would have then been a direct impact on the rheological properties of the granulation fluids, as well as on the subsequent formation of gel layers and erosion properties [18,19]. The literature value reported for viscosity of HPMC (K100LV) is between 80 and 120 mPa s at 20 °C for a 2% solution in water [20]. The average viscosity found here for all 2% HPMC solutions reconstituted from the dry blends and granules approximates to

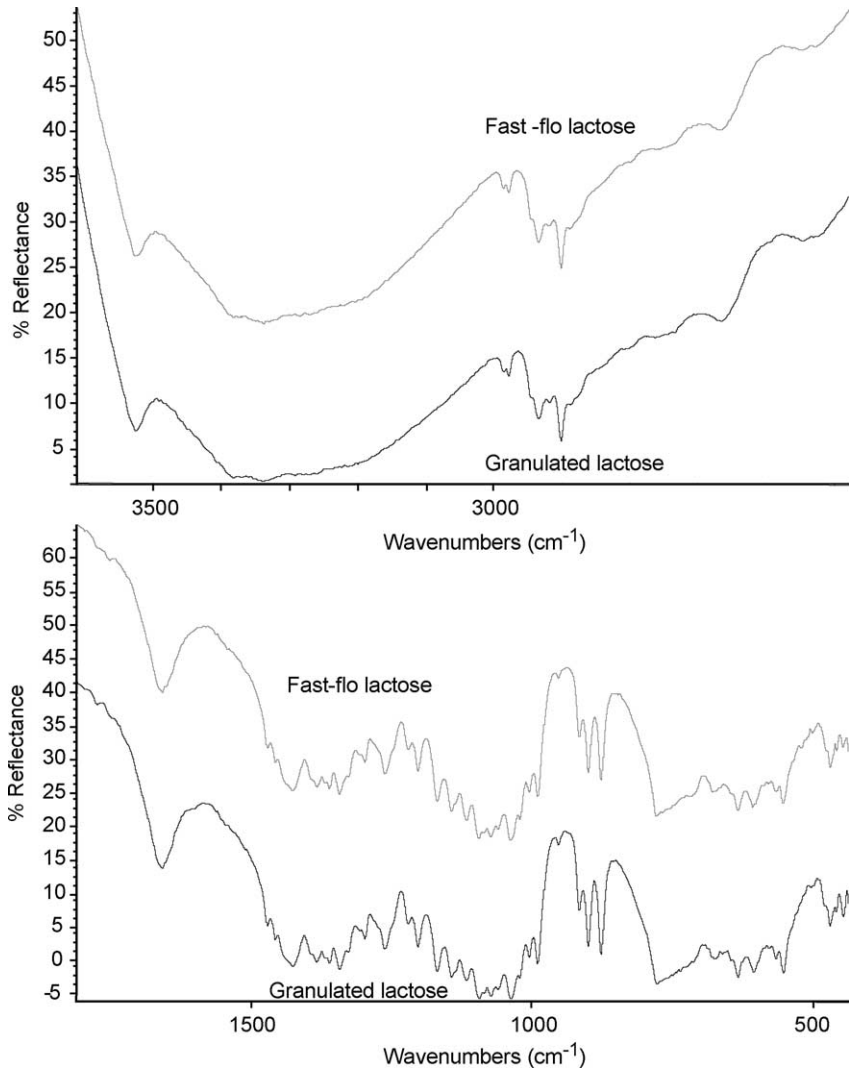

Fig. 3. A comparison of DRIFTS spectra for lactose used in the granulation procedure, pre- and post-granulation. (a) 3600–2400 and (b) 400–1800 cm^{-1}.

this literature value (data not shown). Although there is some lactose present in the system, its contribution to the viscosity is minimal. The data confirms that the wet granulation process does not induce any physical change of the HPMC.

3.6. Scanning electron microscopy

Scanning electron micrographs (Fig. 4) display a distribution of highly visible amorphous cellulosic fibres (HPMC) interspersed with lactose particles in the dry-blend formulations.

When the direct compression formulation comes in contact with water, initially lactose dissolves to leave pores. This leads to 'thinning' of the HPMC and a high degree of polymer chain disentanglement [21], relatively quick erosion of the tablet then occurs. Wet granulation allows an intimate mixture of lactose and partially gelled HPMC granules to form prior to drying. Large uniform granules having distinctive hatchet-shaped lactose particles [22] are indicated for the 15% HPMC formulation (Fig. 5a and b), HPMC is not distinguishable in isolation. In contrast the granules formed with the higher HPMC content (24%) still highlight a distinction between HPMC and lactose (Fig. 5c–f), this is even more apparent at 30% HPMC concentration (Fig. 5e and f). A more homogenous tablet is then prepared at lower HPMC concentrations. Better homogeneity leads to reduced, and/or smaller pore formation at the surface and subsequently less HPMC 'thinning'. Slower erosion of the corresponding erodible tablets, resulting in an increased lag-time following dissolution are observed.

3.7. Dynamic vapour sorption

DVS data indicates that the maximum adsorption of water vapour is much greater for HPMC than for lactose (Fig. 6) due to an increased number of binding sites for water on the hydrophilic polymer chain. It is likely that there is some degree of amorphous to crystalline change in

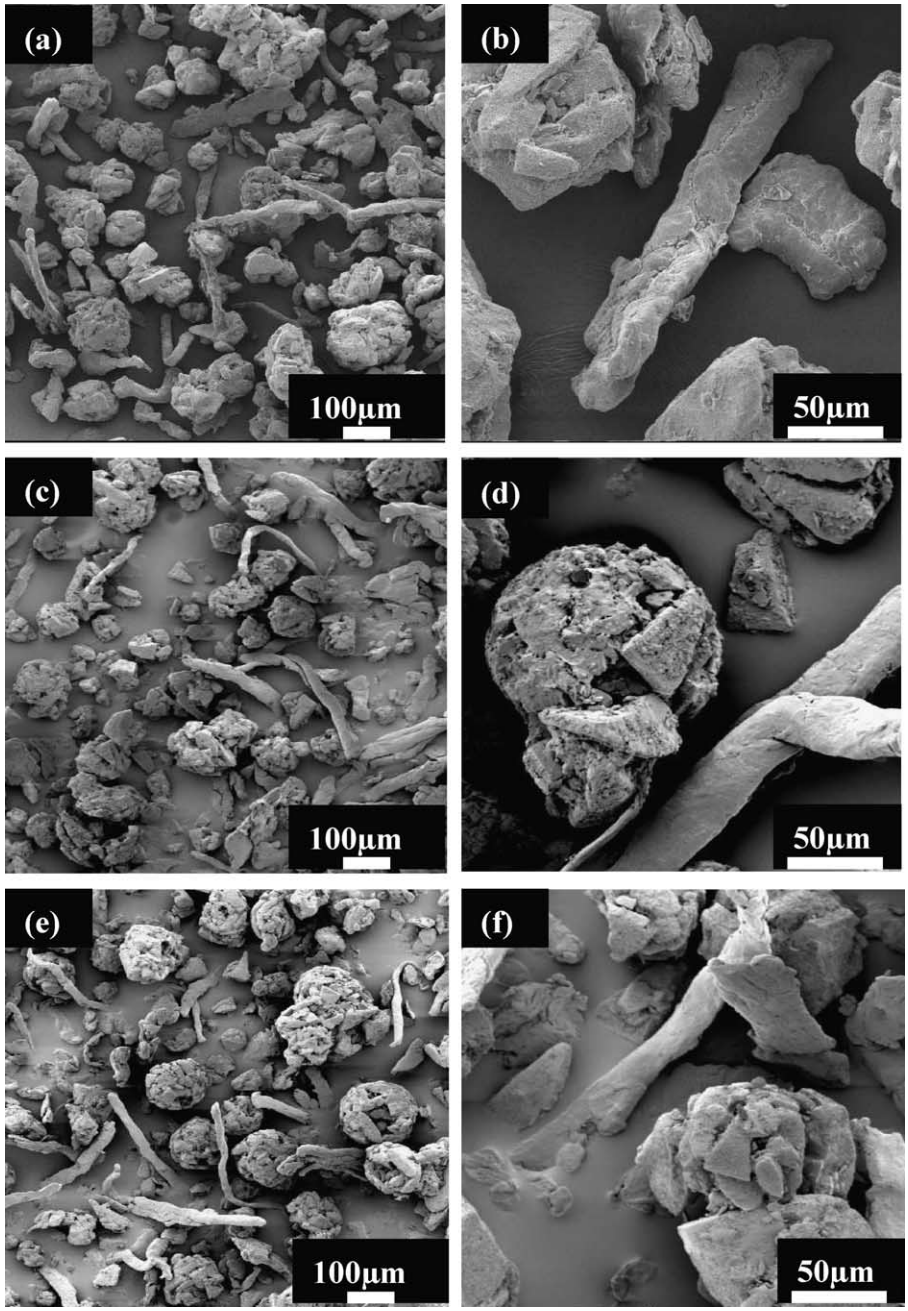

Fig. 4. SEM images of direct compression (DC) formulations prior to tableting indicating homogeneity and dispersion of lactose and HPMC: (a and b) 15% HPMC; (c and d) 24% HPMC; (e and f) 30% HPMC.

the lactose. The Fast-flo grade of lactose used is reported to have a degree of amorphous content which aids powder flow during tableting [23]. Following exposure to a humid environment, such as the granulation process, this amorphous form is likely to change into a crystalline monohydrate form [24]. This could have a contribution to the dissolution performance of the capsule dosage form when initial wetting of the erodible tablet results in a different pore formation and erosion mechanism.

A change in the original mass of the sample is seen post-desorption, and a change in shape is also observed in the lactose isotherm (Fig. 6a) which correlates directly with a glass transition temperature (T_g) [25]. This is consistent with previous studies that suggested that spontaneous crystallisation of lactose occurs when the glass transition temperature of amorphous lactose is lowered by adsorption of water, which serves to act as a plasticizer [26,27]. When the water content approximates 7.25% (at 50% RH) the T_g is lowered to 25 °C, which is also the operating temperature of the DVS instrument. The theoretical weight gain by a purely amorphous sample of lactose is reported to be 5.26% [24]. Using

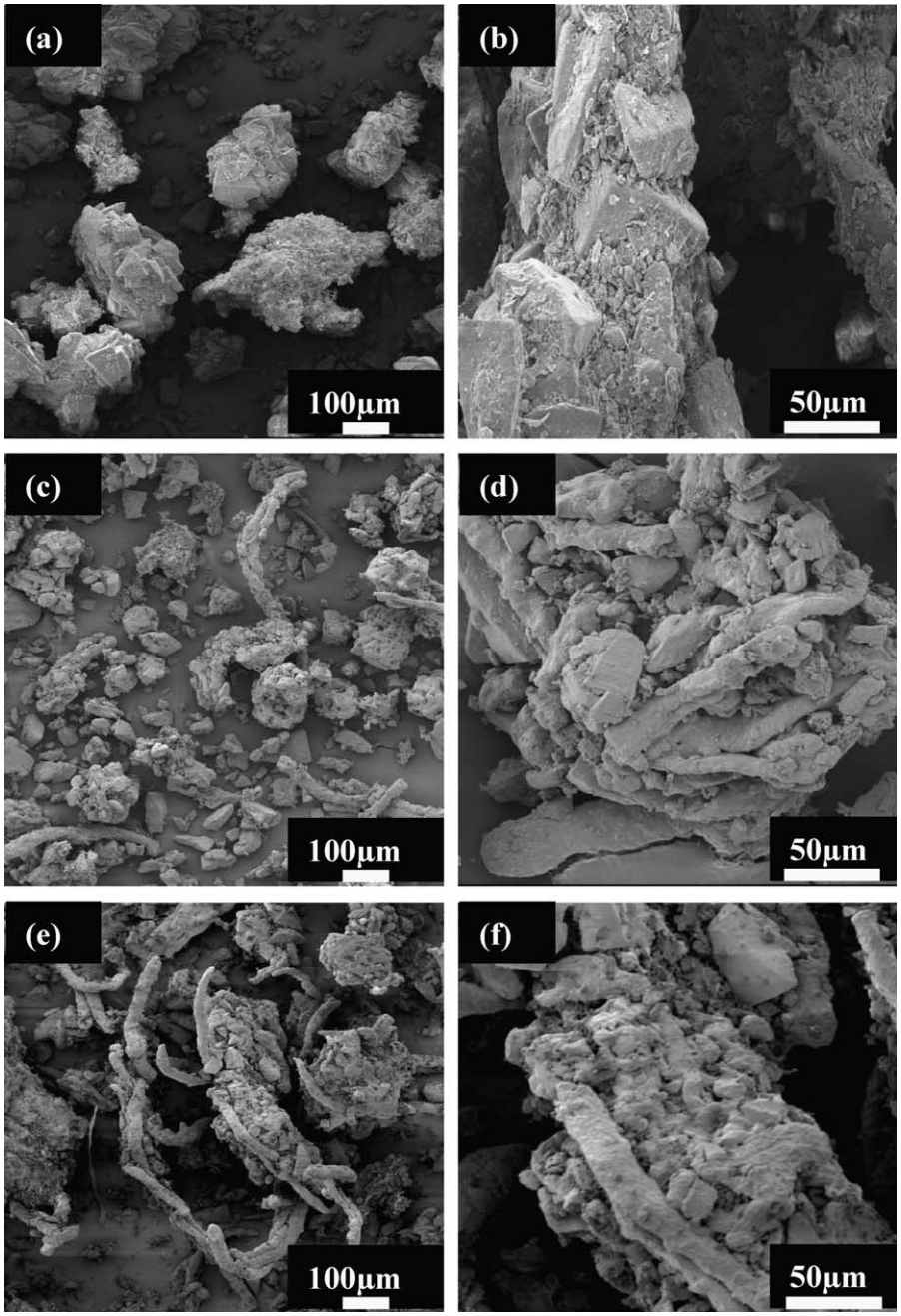

Fig. 5. SEM images of wet granulated (WG) formulations prior to tableting indicating homogeneity and dispersion of lactose and HPMC: (a and b) 15% HPMC; (c and d) 24% HPMC; (e and f) 30% HPMC.

this information the degree of amorphous content can be determined by simple calculation from the DVS data:

$$\text{amorphous content}(\%) = \frac{\text{weight increase}}{5.26} \times 100 \qquad (1)$$

The degree of crystallisation occurring in the sample of Fast-flo lactose can be calculated (Eq. (1)), and indicates there is a 5.46% amorphous content, which is consistent with the spray drying process used to produce the Fast-flo lactose. An amorphous content may also be deduced for direct compression formulations by observing the intercept change of desorption from sorption cycles (data not shown).

Overall moisture weight increases are very low, between 0.06 and 0.3% of the total weight (i.e. 1.33–5.5% amorphous content; using Eq. (1)). The largest difference in moisture weight increase was observed between wet and dry granulations for the 24% formulations. However, this does not show the most significant prolongation of lag-time for the capsule delivery system between the direct compression and the wet granulation erodible tablet formulations. Therefore it is likely any minimal change in

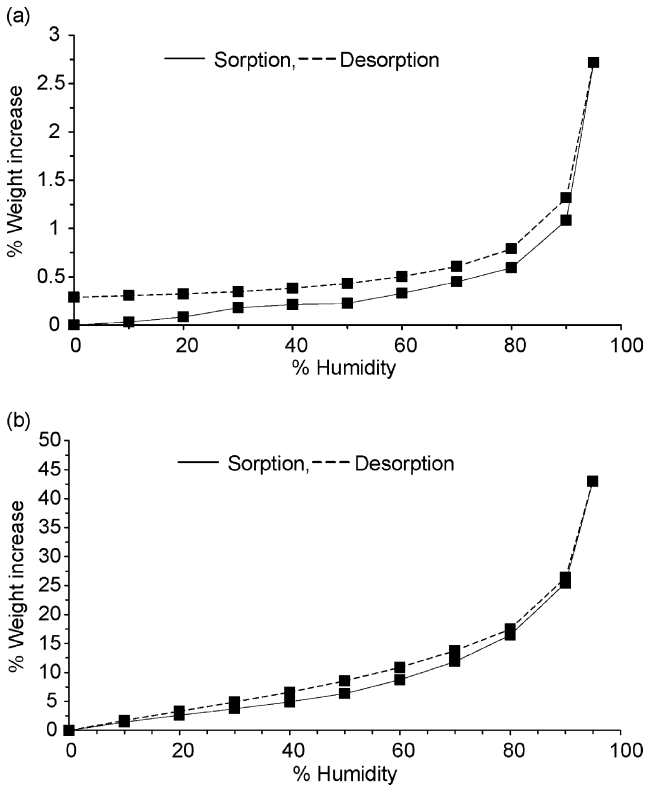

Fig. 6. Water vapour adsorption isotherms for (a) Fast-flo lactose; (b) HPMC K100LV. A net weight gain is observed for lactose following the desorption cycle indicating a transition from amorphous to crystalline lactose.

amorphous content (which may occur during the granulation procedure) is not the cause of the difference in $T_{50\%}$ release from the capsules.

The maximum weight increase indicated that there was a greater adsorption of water with the wet granulated formulations. The smallest change was indicated in the 30% formulations. This suggests that following granulation there is a larger surface area of HPMC exposed and could indicate a coating of HPMC over the lactose, particularly at concentrations lower than 30% HPMC. There is also the possibility that this increase could be due to an overall increase in surface area.

3.8. Microwave dielectric analysis

Microwave dielectric relaxation times of the water dipole are shown to be lowest for the 15% granulated formulation (Table 1) indicating that water is more freely able to move in that less viscous and constrained environment. It therefore follows that the HPMC content of the wet granulated formulation is also able to disperse and disentangle and swell more in this wetted state. The more mobile the system, the greater the disentanglement and gel formation of the HPMC chains during processing. In addition, lactose re-crystallisation (Fig. 5a and b) suggests

Table 1
Water dipole relaxation times for 15, 24 and 30% HPMC wet granulation formulations prior to tableting, determined using the Agilent network analyser

Sample	Relaxation time ($\times 10^{-8}$ ms) % HPMC		
	15	24	30
1	3.267	6.170	6.336
2	2.980	4.956	5.515
3	2.959	5.728	14.228
4	2.698	5.563	6.688
5	2.678	4.812	5.542
6	2.635	5.467	7.662
Average	2.869	5.449	7.662
SD	0.245	0.502	3.314

that at least some of the lactose has dissolved which can lead to its diffusion into the partially disentangled HPMC gel network. Coating of the HPMC around undissolved lactose particles may also occur. When the granulations are dried prior to compression into erodible tablets, the degree of disorder will be fixed in the dried granules prior to tableting. As the dielectric relaxation times are inversely proportional to the degree of disruption to the formulation it would be expected that the fastest relaxation times would lead to an increased change in lag-time delay for the capsule device. This is indeed the case with the 15% HPMC wet granulated formulation showing the greatest variance from the equivalent direct compression formulation.

4. Conclusions

Erodible tablets formulated using a low concentration of HPMC (15%) show a greater prolongation of lag-time following wet granulation than those formulations containing higher HPMC concentrations (24 and 30%). HPMC is unaltered by shear forces involved in the granulation stage and so this processing step can be eliminated as a contributing factor. Although there is evidence of a small amorphous to crystalline transition in the lactose during wet granulation (indicated by the DVS data) there is also no evidence that this has any significant effect on the lag-time. There is no evidence of physical change in the crystalline state as demonstrated by XRPD or DRIFTS analyses. However, water mobility during wet granulation at low concentrations of HPMC (as indicated by the MDA) allows greater chain mobility/swelling and spreading. This results in slower tablet erosion, and hence an increased lag-time of drug release from the time-delayed capsule formulations. This effect reduces the lag-time difference between the wet granulation erodible tablet formulations used in the assembled pulsatile capsule, by increasing the mobility of the polymer chains at low HPMC concentrations (i.e. 15% HPMC) and making a more homogenous mixture prior to

tableting. It has been shown that it is possible to quantitatively examine the extent of hydrophilic polymer spreading within an aqueous system (i.e. during wet granulation) by using the microwave dielectric analysis technique.

Acknowledgements

Thanks to Pfizer Ltd, UK for their contribution of essential materials for the study. Also thanks to the Dow Chemical Company of the USA for gifts of Methocel® and Ethocel® and the Shin-Etsu chemical company of Japan for the gift of the expulsion excipient, L-HPC.

References

[1] H.N.E. Stevens, A. Rashid, M. Bakhshaee, Dispensing device, US Patent, 5,474,784 (1995).
[2] B. Lemmer, Circadian-rhythms and drug delivery, J. Control. Release 16 (1–2) (1991) 63–74.
[3] P. Fantidis, T.P. De Prada, A. Fernandez-Ortiz, A. Carcia-Touchard, F. Alfonso, M. Sabate, R. Hernandez, J. Escaned, C. Bauelos, C. Macaya, Morning cortisol production in coronary heart disease patients, Eur. J. Clin. Invest. 32 (5) (2002) 304–308.
[4] S.K. Gupta, G. Sathyan, Pharmacokinetics of an oral once-a-day controlled-release oxybutynin formulation compared with immediate-release oxybutynin, J. Clin. Pharmacol. 39 (3) (1999) 289–296.
[5] A.C. Ross, R.J. MacRae, M. Walther, H.N.E. Stevens, Chronopharmaceutical drug delivery from a pulsatile capsule device based on programmable erosion, J. Pharm. Pharmacol. 52 (8) (2000) 903–909.
[6] J.C.D. Sutch, A.C. Ross, W. Kockenberger, R.W. Bowtell, R.J. MacRae, H.N.E. Stevens, C.D. Melia, Investigating the coating-dependent release mechanism of a pulsatile capsule using NMR microscopy, J. Control. Release 92 (3) (2003) 341–347.
[7] P. Costa, J. Manuel, S. Lobo, Modeling and comparison of dissolution profiles, Eur. J. Pharm. Sci. 13 (2) (2001) 123–133.
[8] I. Krogel, R. Bodmeier, Development of a multifunctional matrix drug delivery system surrounded by an impermeable cylinder, J. Control. Release 61 (1–2) (1999) 43–50.
[9] Z.T. Chowhan, A.A. Amaro, Y.P. Chow, Tablet-to-tablet dissolution variability and its relationship to the homogeneity of a water-soluble drug, Drug Dev. Ind. Pharm. 8 (2) (1982) 145–168.
[10] P.J. Sheskey, D.M. Williams, Comparison of low-shear and high-shear wet granulation techniques and the influence of percent water addition in the preparation of a controlled-release matrix tablet containing HPMC and a high-dose, highly water-soluble drug, Pharm. Tech. 20 (3) (1996) 80–92.
[11] H. Murakami, T. Yoneyama, K. Nakajima, M. Kobayashi, Correlation between loose density and compactibility of granules prepared by various granulation methods, Int. J. Pharm. 216 (1–2) (2001) 159–164.
[12] J. Siepmann, F. Lecomte, R. Bodmeier, Diffusion-controlled drug delivery systems: calculation of the required composition to achieve desired release profiles, J. Control. Release 60 (2–3) (1999) 379–389.
[13] T.D. Reynolds, S.H. Gehrke, A.S. Hussain, L.S. Shenouda, Polymer erosion and drug release characterization of hydroxypropyl methylcellulose matrices, J. Pharm. Sci 87 (9) (1998) 1115–1123.
[14] G.S. Rekhi, R.V. Nellore, A.S. Hussain, L.G. Tillman, H.J. Malinowski, L.L. Augsburger, Identification of critical formulation and processing variables for metoprolol tartrate extended-release (ER) matrix tablets, J. Control. Release 59 (3) (1999) 327–342.
[15] H.G. Brittain, S.J. Bogdanowich, D.E. Bugay, J. Devincentis, G. Lewen, A.W. Newman, Physical characterization of pharmaceutical solids, Pharm. Res. 8 (8) (1991) 963–973.
[16] J.H. Noordik, P.T. Beurskens, P. Bennema, R.A. Visser, R.O. Gould, Crystal structure, polarity and morphology of 4-o-α-D-galactopyranosyl-α-D-glucopyranose monohydrate (α-lactose monohydrate): a redetermination, Z. Kristallogr. 168 (1984) 59–65.
[17] T. Suzuki, H. Kikuchi, S. Yamamura, K. Terada, K. Yamamoto, The change in characteristics of microcrystalline cellulose during wet granulation using a high-shear mixer, J. Pharm. Pharmacol. 53 (5) (2001) 609–616.
[18] M.C. Bonferoni, C. Caramella, M.E. Sangalli, U. Conte, R.M. Hernandez, J.L. Pedraz, Rheological behavior of hydrophilic polymers and drug release from erodible matrices, J. Control. Release 18 (3) (1992) 205–212.
[19] M.C. Bonferoni, S. Rossi, F. Ferrari, M. Bertoni, R. Sinistri, C. Caramella, Characterization of 3 hydroxypropylmethylcellulose substitution types-rheological properties and dissolution behavior, Eur. J. Pharm. Biopharm. 41 (4) (1995) 242–246.
[20] The Dow Chemical Company, Methocel® Cellulose Ethers, Technical Handbook, McKay, Midland, MI, 1996.
[21] R.W. Korsmeyer, R. Gurny, E. Doelker, P. Buri, N.A. Peppas, Mechanisms of solute release from porous hydrophilic polymers, Int. J. Pharm. 15 (1) (1983) 25–35.
[22] S.L. Raghavan, R.I. Ristic, D.B. Sheen, J.N. Sherwood, L. Trowbridge, P. York, Morphology of crystals of alpha-lactose hydrate grown from aqueous solution, J. Phys. Chem. B 104 (51) (2000) 12256–12262.
[23] A.H. Kibbe, Lactose, in: A.H Kibbe (Ed.), Handbook of Pharmaceutical Excipients, American Pharmaceutical Association, Washington, DC, 2000, pp. 1739–1740.
[24] G. Buckton, P. Darcy, The Use of gravimetric studies to assess the degree of crystallinity of predominantly crystalline powders, Int. J. Pharm. 123 (2) (1995) 265–271.
[25] J. Zhang, G. Zografi, The relationship between BET- and free volume-derived parameters for water vapor absorption into amorphous solids, J. Pharm. Sci 89 (8) (2000) 1063–1072.
[26] P. Darcy, G. Buckton, The influence of heating/drying on the crystallisation of amorphous lactose after structural collapse, Int. J. Pharm. 158 (2) (1997) 157–164.
[27] G. Buckton, P. Darcy, Water mobility in amorphous lactose below and close to the glass transition temperature, Int. J. Pharm. 136 (1–2) (1996) 141–146.