International Journal of Pharmaceutics 404 (2011) 142–147

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Monitoring of swelling of hydrophilic polymer matrix tablets by ultrasound techniques

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ARTICLE INFO

Article history:
Received 9 August 2010
Received in revised form
11 November 2010
Accepted 12 November 2010
Available online 19 November 2010

Keywords:
Ultrasound
Tablet
Swelling
Erosion
Gel layer
Hydroxypropyl methylcellulose (HPMC)
Polyethylene oxide (PEO)

ABSTRACT

The aim of this study was to investigate the ability of ultrasound (US) techniques to monitor the swelling behaviour of hydrophilic polymer matrix tablets. Tablets were prepared from hydroxypropyl methylcellulose (HPMC) and polyethylene oxide (PEO) polymers. The movement of the eroding front was investigated with ultrasound scanning techniques on each tablet's outer interface during tablet immersion in phosphate buffer (PB). In addition, a US window technique was utilized to simultaneously evaluate eroding and swelling front movements during the tablet dissolution process. An optical monitoring was used as the reference method. The focused pulsed echo ultrasound method was found to be applicable for evaluating the swelling process of hydrophilic polymer matrix tablets. Furthermore, it was noted that the sensitivity to follow hydrogel formation and thickening by US monitoring varied depending on the polymer under study. Thus, multifront detection is challenging since the hydrogels formed by different polymers may have totally different acoustic properties. It was found that the microbubbles formed inside the hydrogel were acting as a "contrast agent", characteristic of some polymers during immersion. In spite of these challenges, the US window technique introduced in this study was proven to be a promising method for simultaneous multifront detection.

1. Introduction

Swellable matrix tablets have become popular as drug delivery technologies because of their ability to regulate drug release kinetics and relatively simple manufacturing process (Varma et al., 2004). The monolithic systems can be prepared by compression of a powdered mixture of a drug and additional excipients. Drug release from swellable matrix tablets is strongly associated with the swelling and dissolution characteristics of the hydrophilic polymer, i.e., the formation and erosion of an outer gel layer on the matrix surface (Harland et al., 1988; Colombo et al., 1995, 1996, 1999, 2000; Siepmann and Peppas, 2000; Siepmann et al., 2002; Borgquist et al., 2006).

Exposure to biological fluids in the gastrointestinal tract causes the liquid penetration into the dry tablet matrix evoking an abrupt change of the hydrophilic polymer from the glassy to the rubbery state. At the time, a sharp boundary appears between the glassy and rubbery regions, i.e., the swelling front. The total volume of the tablet increases due to polymer swelling and a boundary between the polymer matrix and the surrounding medium, called the erosion front becomes detectable (Lee and Peppas, 1987). These two physically evident fronts define in detail the tablet gel layer.

During the drug release process the gel layer thickness as well as its structure and composition experiences a continuous change. With time, the swollen gel layer becomes sufficiently hydrated for erosion or dissolution to take place. The swelling behaviour of the tablet matrix can mechanistically be described by the movement of the swelling and erosion fronts. Inside the gel layer, a third front may also exist separating the undissolved drug from the dissolved (Lee and Kim, 1991). The drug release is controlled by the dissolved drug diffusion through the gel layer and/or by erosion of the gel layer. Therefore, there has been increasing interest focused on objective methods for qualitative and quantitative analysis of erosion and swelling front characteristics.

There are several published methods for monitoring the gel front movements which are specific to swelling behaviour and drug release processes. Optical monitoring of a swelling tablet as a simple method for gel layer thickness determination was introduced by

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doi:10.1016/j.ijpharm.2010.11.026

Colombo et al. (1987). A dissolving tablet was placed between two transparent Plexiglas® sheets and the hydrogel layer formation was monitored from the axial direction of the sample. Slightly modified methods based on optical tablet structure estimation have been utilized as applied research tools (Gao and Meury, 1996; Ferrero et al., 2000; Bajwa et al., 2006). In addition to the optical methods, Kazarian and van der Weerd (2008) used FTIR imaging to observe the same phenomenon. However, the swelling rate of axially compressed hydrophilic tablets is not usually isotropic and the tablets tend to swell more axially than radially in non-restricted immersion (Gao and Meury, 1996; Zuleger et al., 2002). It should also be noted that optical monitoring is often dependent on there being a clear pathway for vision which limits the use of the technique in opaque medium.

Other widely published methods to monitor the structural changes of matrix tablets based on hydrophilic polymers are nuclear magnetic resonance (NMR) imaging and NMR spectroscopy (Rajabi-Siahboomi et al., 1994; Kowalczuk et al., 2004; Baumgartner et al., 2005; Mikac et al., 2007; Abrahmsén-Alami et al., 2007; Tajarobi et al., 2009; Fyfe and Blazek, 1997; Dahlberg et al., 2007). NMR can be used to monitor hydrogel formation process and even the water concentration gradient of gel layers can be detected. However, the cost for the high quality magnets, which are an integral part of this equipment, may restrict the applicability of this technique for routine measurements.

Konrad et al. (1998), used ultrasound (US) to estimate the swelling of hydroxypropyl methylcellulose (HPMC) matrix tablets as an alternative to traditional dissolution tests and found that both methods gave nearly the same results about the eroding front displacement. It was proposed that the erosion front displacement may be monitored by measuring the echo of pulsed ultrasound beam at 10 MHz frequency. However, the swelling front was not detectable by ultrasound. Luprano et al. (2000) used US pulse-echo technique to measure hydrogel water sorption and monitored the advancement of the swollen–unswollen fronts of polymer films. The changes in ultrasonic attenuation were attributed to alterations in the reflections from the swollen–unswollen boundary, microvoids scattering and absorption of the ultrasonic waves due to the glass to rubber transformation. Yochev et al. (2006), presented results from speed of sound and attenuation studies of various polymers with through-transmission geometry. The hydrophilic polymer samples were considered as excellent US couplants transmitting the high frequency US and therefore US wave penetrates such materials effectively. As far as we are aware, the study of Konrad et al. (1998), is the only publication where pharmaceutical hydrophilic tablet swelling has been determined by US. However, the method is widely used in non-destructive testing (Kundu, 2004) and it has also been used to investigate biological and non-biological multilayered structures (Revonta, 1980; Wendt et al., 1996; Kundu, 2004).

The aim of the present study was to investigate the feasibility of ultrasound pulse echo scanning techniques in monitoring swelling behaviour processes in hydrophilic matrix tablets. For this purpose, two different US measurement methods and one reference method based on optical examination were tested.

2. Materials and methods

2.1. Sample preparation

One hydroxypropyl methylcellulose (HPMC) and two polyethylene oxide (PEO) polymers with different molecular weights were used. The HPMC used was of USP grade 2910 (type 60 SH) produced by Shin-Etsu Chemical Co. Ltd. (Tokyo, Japan). The viscosity grade of the HPMC was 4000 cP corresponding to weight average molar masses, Mw, of 3.6×10^5 g/mol. The average number of methoxyl groups attached to the anhydroglucose unit of HPMC 2910 was, according to the supplier, 1.9 (corresponding to 28–30 wt.%) and the average number of mols of hydroxypropoxyl groups per mol of anhydroglucose unit of HPMC was 0.25 (corresponding to 7–12 wt.%). The PEO polymers used were Polyox WSR N-10 and Polyox WSR N-60K by Dow (Wien, Austria) corresponding to PEO0.1 and PEO2.0 used by Körner et al. (2005), Abrahmsén-Alami et al. (2007) and Körner et al. (2009). All powders were stored in sealed containers over anhydrous silica to maintain the moisture content at a low constant level. The powders were used as received without sieving or any other pre-processing. Tablets (300 mg for HPMC and 315 mg for PEO) were directly compressed with a compaction simulator (PCS-1, Puuman Oy, Kuopio, Finland) by using flat-faced punches of 10 mm in diameter. No lubrication was used. Compaction profiles were sinusoidal for both upper and lower punches. Different filling depths and amplitudes were applied to achieve tablet heights of 4.0 and 3.7 mm for HPMC and PEO tablets, respectively. After compaction, the tablets were stored with anhydrous silica for at least 20 h prior to further characterization.

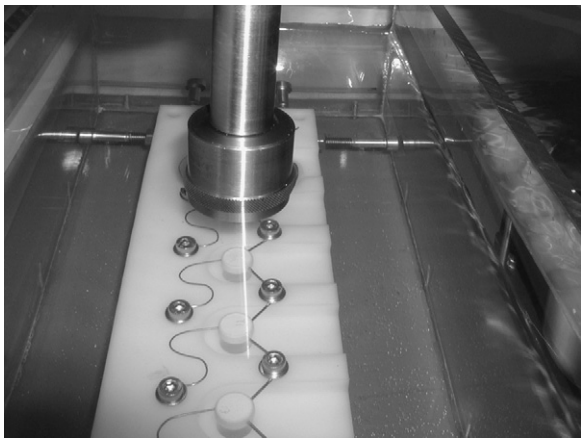

Fig. 1. The sample holder for six tablets placed in the polycarbonate tank used for dissolution testing. Ultrasound probe can be seen on the top scanning a line of immersed tablets.

2.2. Acoustic measurements

All acoustic measurements were conducted using an UltraPAC-system (Physical Acoustics Corporation, Princetown, NJ, USA) which consisted of a tank and 3D-scanning drives, a high frequency A/D-board (PAC-AD-500) and focused broadband ultrasound transducers (Panametrics V307, Panametrics Inc., Waltham, MA, USA; center frequency = 5 MHz, frequency range (−6 dB) = 3.3–6.7 MHz, focal length = 50 mm, beam diameter of 0.6 mm). The measurements were done using the pulse-echo (PE) geometry with 62.5 MHz sampling frequency. The ultrasound pulser voltage, damping and energy level were set to 400 V, 2000 Ω and 103 μJ, respectively. The detected US signal was digitally filtered with a third order (18 dB/octave) Butterworth 0.05–10 MHz band-pass filter.

2.2.1. Direct eroding front measurement

Six identical samples with similar structural characteristics were measured simultaneously in each test. Samples were set into a line with a distance of 30 mm between the center points of the samples. In addition, there were two polished stainless steel reference plates at each end of the sample line. The sample surfaces were adjusted to a distance similar to the focal length of the US transducer with a custom made sample holder (Fig. 1). The chosen time points for ultrasound measurements were 0, 10, 30, 60, 120,

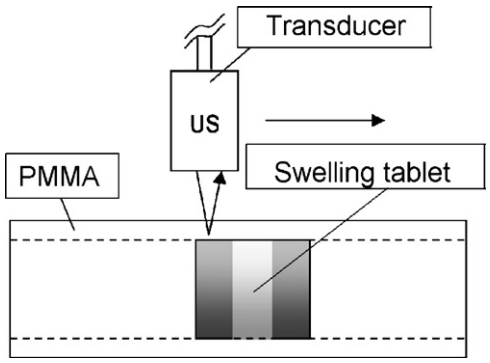

Fig. 2. A schematic illustration of the ultrasound window setup: ultrasound transducer (US) scanning parallel to the axis of the sample tablet located in a transparent acrylic (PMMA) block acting as an ultrasonic window. The hydrogel layers and the dry core of a swelling tablet can be detected as a function of the scanning location.

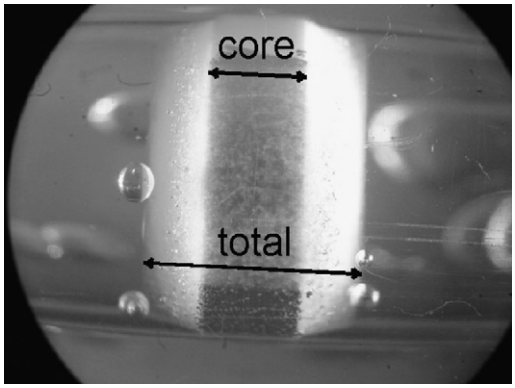

Fig. 3. Determination of tablet structures by optical monitoring used as the reference method.

180, 240 and 480 min. The speed of sound was measured in 0.1 M phosphate buffer (PB, pH 6.8), as specified in the PhEur, in order to convert the time of flight information into spatial information. The tablets were immersed into degassed (air concentration < 1.0 ppm) PB. Acoustic measurements were conducted at room temperature 24 ± 1 °C and the measurement time, i.e., total of 8 h, was used in all tests. All the tablets were line scanned along the tablet diameter using the ultrasound pulse-echo measurement mode to investigate the eroding front movement. The distance between the samples and the US transducer was 50 mm at the beginning of the immersion. The measurement data was recorded with custom made LabView™ 6.5 (National Instruments, Austin, TX, USA) software and stored for off-line analysis. The signal envelope was determined by utilizing the Hilbert transform. The maximum of the signal envelope, i.e., reflection from the interface between two materials (PB-eroding front), was used to define the correct time of flight, t. The distance d between the sample surface and the transducer was determined by using the recorded time of flight and the predetermined speed of sound c in the medium:

$$d = c\frac{t}{2} \quad (1)$$

The PE measurement data was used to determine the topologic data, or surface placement, of the line scanned. The vertical location of the eroding front was determined from the sample surface at each time point for six identical tablets. An average of 10 subsequent signal echoes was used at each measurement point. The normalized reflection amplitude A_n, was determined by normalizing reflection amplitude of the sample A_s, with the corresponding reflection A_r, measured from polished stainless steel plate:

$$A_n = \frac{A_s}{A_r} \quad (2)$$

2.2.2. US window measurement for gel layer thickness

The acoustic determination of swelling and eroding front movement was investigated for all polymer tablets. The sample holder was made of a polymethylmetacrylate (PMMA) rod, 30 mm in diameter and 70 mm in length (Fig. 2). PMMA was chosen as a transparent material with appropriate acoustic properties (Yochev et al., 2006). A hole with 10 mm diameter was drilled axially through the rod. The upper surface of the rod was flat milled to obtain a flat faced interface for the ultrasound measurements and visual camera monitoring and also in order to minimize the ultrasound scattering within the US window. The contact with PB was restricted to the parallel flat faced surfaces of the tablet samples during immersion. The distance between the transducer and the sample was set to the focal length of the transducer to achieve maximal intensity from the distance of PMMA-sample interface. The US scanning step size was 0.1 mm and the US beam orientation was set to be parallel to the sample radius. The PE signals were recorded along the tablet axis and fast Fourier transform (FFT) was used for spectral calculation as a function of the scanning location. The eroding and swelling front displacement were determined by using the first order derivative of the US echo intensity at 3.4 MHz frequency, which was observed to provide the highest sensitivity for the application, this being chosen after preliminary experiments conducted with the transducer. Finally, the US window measurement was compared to front displacement data obtained by optical monitoring. The optical estimation of the swelling and eroding front location was obtained by microphotography. The sample was photographed through an Olympus SZ-60 stereomicroscope (Olympus Optical Co. Ltd., Tokyo, Japan) with an Olympus C-5050 digital camera (Olympus Optical Co. Ltd., Tokyo, Japan). The photographs at the set time points were analyzed by using the measurement tool of Gimp v2.1–software (http://www.gimp.org). The thickness of the tablet structures was measured from those microphotographs from which the gel layer and dry core of the tablet could be clearly seen (Fig. 3). The optical measurement was made and used as a reference method for the US window method.

3. Results and discussion

The speed of sound, v, measured in the phosphate buffered solution at room temperature (24 ± 1 °C) was 1578 ± 19 m/s. The eroding front displacement during tablet immersion was evaluated for HPMC and PEO based tablets as shown in the Fig. 4A–C. The dry core and the gel layer of the HPMC tablets remained intact at the last measurement point, where the total eroding front displacement was determined to 2.5 ± 0.4 mm. The PEO0.1 tablets swelled rapidly and dissolved totally within 120 min. The PEO2.0 tablets sustained during the observation time and had an eroding front displacement of 1.7 ± 0.5 mm measured after 8 h. Normalized reflection amplitude, A_n, decreased as a function of time with all polymers tested (Fig. 4D–F). This is related to tablet's medium absorption and the change of the acoustic properties due to immersion of PB. The HPMC absorbed PB slower within the first 120 min compared with the PEO2.0. The plateau region of absorption was reached at 240 and 120 min with HPMC and PEO2.0, respectively. PEO0.1 appeared to have an almost constant decay of the normalized reflection amplitude indicating a constant rate of PB absorption. PEO0.1 tablet size decreased continuously as a result of tablet hydration (Fig. 4C) indicating a very fast dissolution process. For PEO2.0, the eroding front moved outwards initially very slowly although the gel layer was observed visually to rapidly become thicker indicating that the swelling process is faster than the erosion process. These results are qualitatively in agreement with the recently published finding

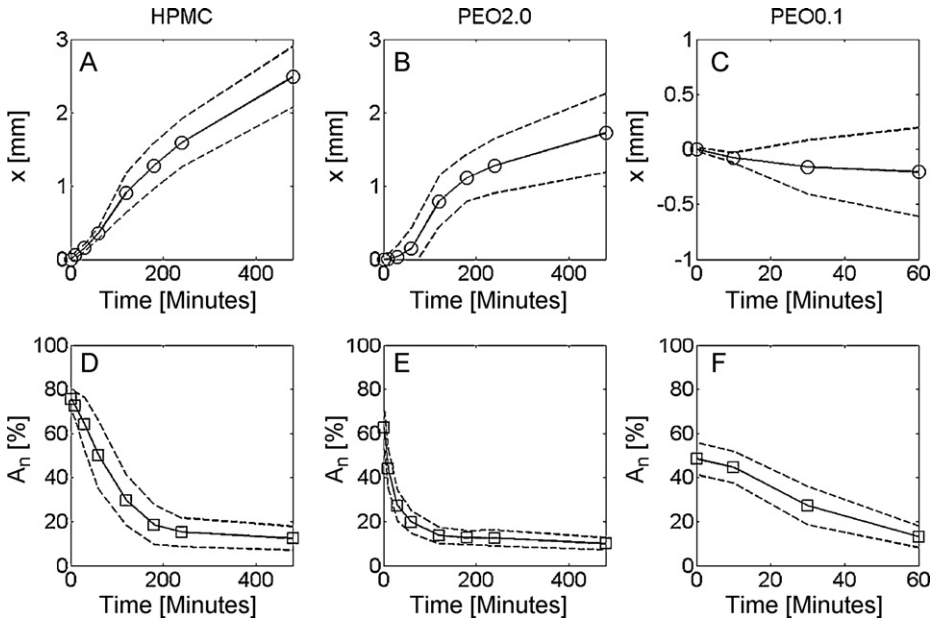

Fig. 4. The eroding front movement (A–C) and the normalized reflection amplitude (D–F) as a function of time. The mean (solid line) and standard deviation (dashed line) of 6 samples at each time point is presented.

of Körner et al. (2009), conducted using rotating disk technique and distilled water medium. According to Fig. 4C, the total thickness of PEO0.1 decreased already in the beginning of the process and the sample surface absorbed 50% of the US pulse amplitude instantly at the starting point. This might have indicated rapidly progressing swelling or acoustic matching of the buffer-gel and gel-core layers, which could have led to decreased capability for the layer interface to reflect US echoes. To clarify the issue, the beginning of the dissolution process was monitored with digital camera in degassed PB. Interestingly, it was observed that microscopic gas bubbles had become entrapped inside the HPMC gel layer during immersion (Fig. 5). These bubbles might reflect the US beam, preventing it from penetrating into the deeper structure of the tablet, i.e., the swelling front. This phenomenon was not evident for tablets based on PEO. The lack of microbubbles during formation of the PEO hydrogels might have resulted a false identification of the interface (Fig. 4B and C). One might hypothesize that the interface detected via the echo is the swelling instead of the erosion front, as seen in Fig. 4C, where PEO0.1 eroding front moves in negative direction. This may be explained with the detected echo being formed by the swelling front instead of the eroding front, because of the equal acoustic properties of the PEO0.1 gel layer and the PB medium.

The results from the US echo measurement suggest that the method is suitable to be used non-invasively to study the swelling of hydrophilic polymers and give real-time size information. However, the structural investigation was restricted to outer surface as that was also observed by Konrad et al. (1998). The US window method was developed in order to probe both the swelling and the erosion fronts simultaneously. The fronts defining the gel layer was determined by using the derivative of the US amplitude measured as a function of time. The 3.4 MHz frequency was the most sensitive for the detection and thus it was chosen in the subsequent analyses. Systematic difference was found in the HPMC eroding and swelling front movement, as measured with US window and optical reference methods (Fig. 6). The positions of the fronts determined by US are 0.6–1.0 mm smaller than those of determined with the optical method. However, the gel layer thicknesses (Fig. 6) determined using the two different methods were highly similar. Therefore, the systematic difference in determination of front positions may be attributed to the US beam in use, since the beam diameter minimum is 0.6 mm. The HPMC gel layer thickness at 4 h was 4.9 ± 1.0 mm and 5.5 ± 1.0 mm (Fig. 6) by US window and optical method, respectively. Even though, there were difficulties to measure the eroding front displacement with both methods, the swelling front movement results were found to coincide. It can be seen in Fig. 7, that the low viscosity gel layer of PEO0.1 starts to flow off after 20–120 min. In this case, the eroding front movement was faster during the optical measurement compared with the US method and the gel layer thickness measured with US was nearly two times larger than that of measured with the optical method. The geometry used in US window method was found challenging to use with low viscosity grade PEO0.1. The gel layer formed

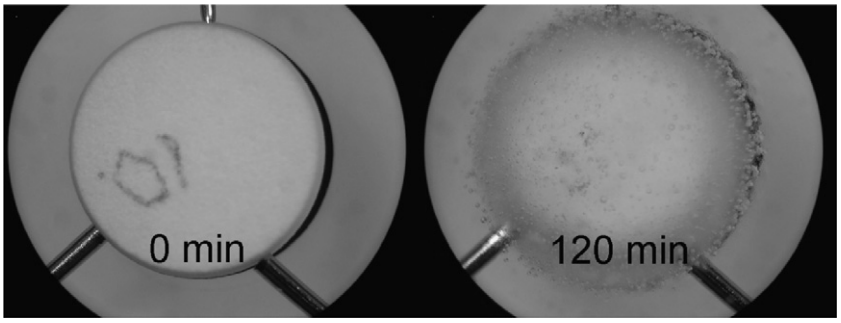

Fig. 5. A detailed view of HPMC tablet gel at start of the immersion and after two hours of swelling in distilled water. Microbubbles can be seen forming inside the gel.

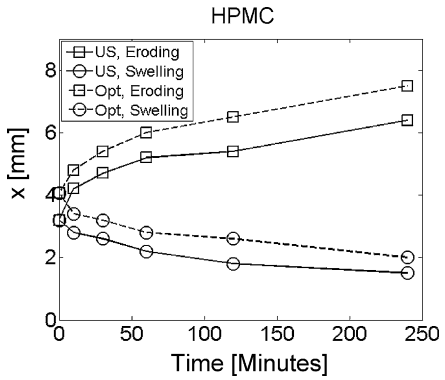

Fig. 6. The displacement curves of the eroding front (squares) and swelling front (circles) of HPMC as a function of time measured with US window (solid line) and optical (dashed line) methods. The gel layer thickness is equal to the distance between the eroding and swelling front locations.

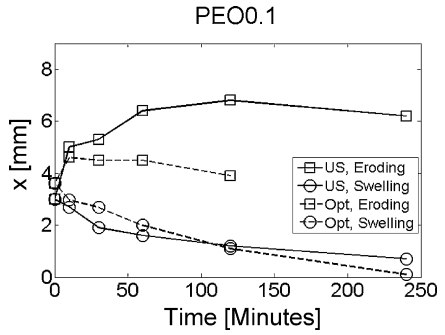

Fig. 7. The displacement curves of the eroding front (squares) and swelling front (circles) of PEO0.1 as a function of time measured with US window (solid line) and optical (dashed line) methods. The gel layer thickness is equal to the distance between the eroding and swelling front locations.

by PEO0.1 resembled more a viscous fluid than a rubbery gel and thus, the gel layer thickness determination of PEO0.1 was considered to be challenging, even for the optical investigation. Even so, the results obtained with PEO0.1 (Figs. 4 and 7) are similar to the data published by Körner et al. (2009), where PEO0.1 tablets dissolved totally within 2–3 h in distilled, 25 °C water. It is shown that the US window method gave values for the erosion front positions that were significantly lower than those determined with the optical method and the gel layer thickness is underestimated by one third (Fig. 8). However, the US window measured swelling front displacement results were nearly similar to the results with the

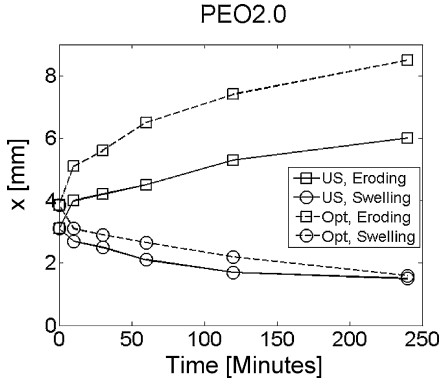

Fig. 8. The displacement curves of the eroding front (squares) and swelling front (circles) of PEO2.0 as a function of time measured with US window (solid line) and optical (dashed line) methods. The gel layer thickness is equal to the distance between the eroding and swelling front locations.

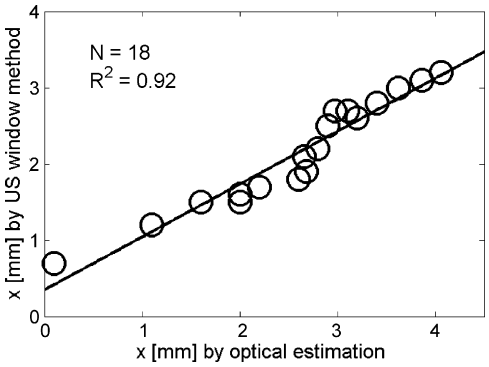

Fig. 9. Correlation between ultrasound window method and optical swelling front estimation.

optical method for all polymers used in the study. There was a systematic difference of 0.6–0.8 mm between US window and optical measurement values at the beginning of the measurements. This was likely result of the transducer characteristic axial resolution, i.e., the beam diameter of 0.6 mm.

In the US window, the geometry was restricted and blocked the solution to penetrate only into the flat faces of polymer tablet which was not the case in the original US echo measurement. Thus, the measurement geometries of the methods were different and the results cannot be compared one-to-one. However, qualitative correspondence between the methods was obtained, and strong correlation ($R^2 = 0.92$) was found between the values obtained with the ultrasound window and optical method in the detection of swelling front for all polymers used in the study (Fig. 9). Therefore, it is suggested that the US window method is suitable technique for determining the inner structure of hydrophilic swelling polymers.

Another point to be considered is related to the detection of the interface between the inner (glassy) core and the swelling polymer gel. The spatial resolution of the US beam at a wavelength of 3.3–6.7 MHz is approximately 250–500 μm in a water-like medium. The thickness of the gel layer is only a few millimeters at its maximum. Although it is possible to measure detectable echoes from both interfaces (medium-gel and gel-core), echoes may (partially or completely) overlap due to limited spatial resolution, especially during the early stages of polymer swelling when only a thin gel layer is observed. In addition, a part of the signal is reflected and scattered depending on the differences in the acoustical impedance between the materials, the heterogeneity of the gel layer and the propagation direction of the beam compared to the interface. These are factors that are dependent on the investigated material and may limit the use of the method in some applications. Using transducers with proper frequency range and focusing parameters, one might overcome these limitations and tune the transducer properties to be adequate for any particular application.

4. Conclusions

Ultrasound has been traditionally used for detecting interfaces between materials of clearly different acoustical properties. The size of the detectable object is determined by the wavelength of the ultrasound beam. As a conclusion, ultrasound could be used to follow the swelling process of hydrophilic polymer tablets. However, the polymers to be studied must possess certain acoustic properties in order to make the medium-polymer interface detectable. These properties depend on the used US frequency in use. The direct US pulse echo method was highly challenging when used for simultaneous detection of the both, eroding and swelling fronts, whereas US window is more suitable for this due to the design of measurement geometry where all the layers are detectable with US

beam.

In summary, the detection of the swelling front is more challenging than the eroding front. It was found that the US window technique introduced in this study was a promising method for simultaneous multifront detection.

Acknowledgements

The help of Professor Jukka Jurvelin offering his research groups laboratory facilities for the ultrasound measurements is gratefully acknowledged. The authors acknowledge Mr. Matti Timonen for technical software issues and Mrs. Päivi Tiihonen and Mr. Jarkko Leskinen for their practical laboratory work. Finally, Mr. Juhani Hakala's contribution to manufacturing and customizing of the sample holders is greatly appreciated. AstraZeneca is acknowledged for financial support during the experimental work.

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