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The use of ultrasound and penetrometer to characterize the advancement of swelling and eroding fronts in HPMC matrices

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Abstract

The determination of gel layer thickness and the velocity of front movement in Hydroxypropylmethylcellulose (HPMC) matrices which contain both a freely and a poorly soluble drug, respectively, is described. A new method based on the measurement of backscattered ultrasound signals has been developed for characterizing advancement of eroding front. The advantage of the ultrasound method is the possibility of continuous measurements. Our investigations indicate that both methods achieve nearly the same result. Matrices with pholedrine sulphate showed greater movements of the eroding front compared to matrices with chloramphenicol, whereas the movement of the swelling front was almost the same in each case. The drug release is dependent on the solubility of the drug, therefore the diffusion of the drug through the gel and therefore the position of the diffusion front in the gelling zone can be considered a possible descriptor of drug release from HPMC matrices.

Keywords: Hydroxypropylmethylcellulose; Swelling front; Eroding front; Penetrometer; Ultrasound

1. Introduction

HPMC are hydrophilic cellulose ethers which have been utilized in investigating drug release from matrices containing both freely water soluble and poorly water soluble drugs (Christensen and Dale, 1962; Lapidus and Lordi, 1966, 1968; Ford et al., 1985a,b,c). The principle of drug release from matrix tablets is that on exposure to an aqueous medium the tablet surface becomes wet and HPMC starts to hydrate forming a gel layer. After an initial burst of soluble drug from the surface an expansion of the gel layer follows when water penetrates into the tablet. Therefore, thickness of the gel layer increases and thus acts as a diffusion barrier. If the outer layers become

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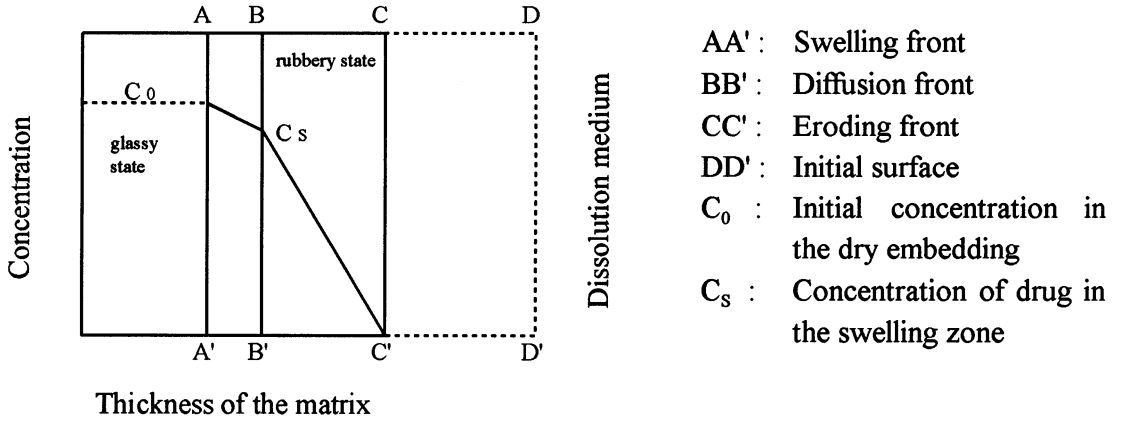

Fig. 1. Simplified model of moving fronts during swelling of HPMC matrix (modified by Colombo et al., 1987; Colombo, 1993; Harland et al., 1983, respectively).

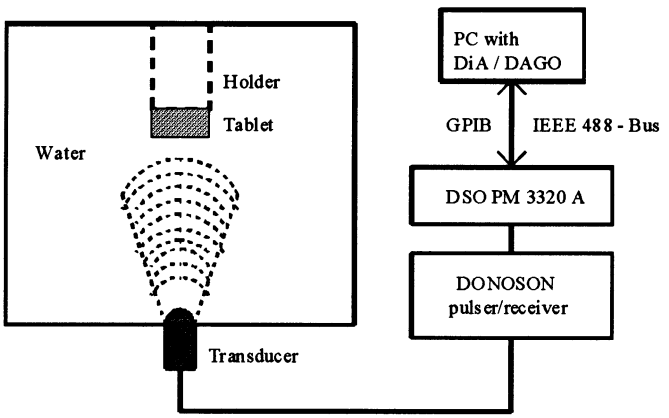

Fig. 2. Apparatus for ultrasound measurement of swelling and eroding front advancement.

fully hydrated they dissolve. This process is referred to as erosion. Drugs are released by a combination of two mechanisms (Huber et al., 1966; Alderman, 1984): diffusion through and attrition of the gel layer, where water soluble drugs were released by diffusion out of this layer and by erosion of the gel, whereas, poorly soluble drugs were mainly released by erosion. The release mechanism from polymer matrices is affected by the aqueous solubility of a drug. The kinetics of drug release were examined for both freely soluble (Higuchi, 1962) and poorly water soluble drugs (Higuchi, 1963). Korsmeyer et al. (1983) found a simple relationship which may be used to describe drug release from polymeric systems. Several investigators have examined the influence of different factors (Ford et al., 1987; Feely and Davis, 1988; Wan et al., 1991) and considered several possible ways to determine the rate of drug release from gelling matrix tablets (Bamba et al., 1979). Especially the diffusion of drug through a gel layer of constant thickness is proposed as a controlling step by a number of investigators (Lee, 1980; Baveja et al., 1987; Colombo et al., 1987). The latter concluded that the thickness of the gel layer was a function of time resulting from the amount of liquid penetrating into the matrix. Water penetration may be described as a diffusion front moving into the tablet. The physical situation in a hydrophilic swellablesoluble polymer matrix is characterized by three fronts (Fig. 1).

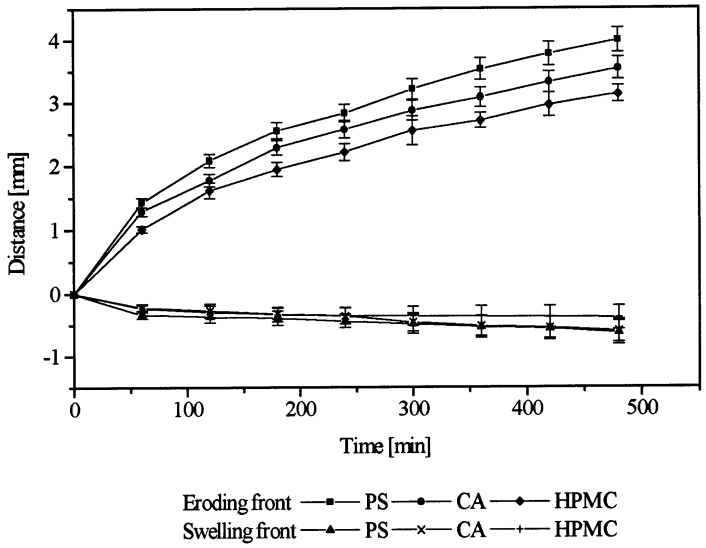

Fig. 3. Swelling and eroding front position of HPMC matrices with (PS, CA) and without model drugs (HPMC) at 50 rpm.

The transition of the polymer from the glassy state to the rubbery state occurs on the swelling front at the core of the matrix. The boundary between dissolution medium and matrix surface is designated as eroding front. Finally, the transition of the drug from the solid drug to solution occurs on the diffusion front.

During the drug release from such hydrocolloid systems, the swelling and diffusion front move inwards and the eroding front moves outwards on the swollen polymer. The advance of the swelling and eroding front in the same direction can lead to a synchronization of velocity of the front movement. The result of such phenomena is a constant drug release.

The purpose of this study is to examine the dynamics of front movement in HPMC matrices with both freely and poorly water soluble drugs.

Table 1
Rate of movement of the swelling and eroding front of pholedrine sulphate matrices at different hydrodynamic conditions

Stirring speed (rpm)	Velocity of front movement (mm/h)	r
Eroding front		
0	0.3625	0.993
50	0.3534	0.994
100	0.2977	0.999
150	0.2676	0.998
Swelling front		
0	0.0316	0.986
50	0.0357	0.995
100	0.0422	0.993
150	0.0473	0.995

2. Materials and methods

2.1. Materials

Pholedrine sulphate (PS), AB-DDR and chloramphenicol (CA), AB-DDR, were chosen as model drugs to represent water soluble and poorly water soluble drugs, respectively. Methocel® K 4 M Premium (Colorcon Ltd., Orpington, UK) was used as matrix polymer. Degassed and distilled water was used as the penetrant.

2.2. Methods

2.2.1. System preparation and front advancement measurements with the penetrometer

Unless stated all the tablet formulas that were prepared contained 10% of the model drug and 90% HPMC. The drug was mixed with the poly-

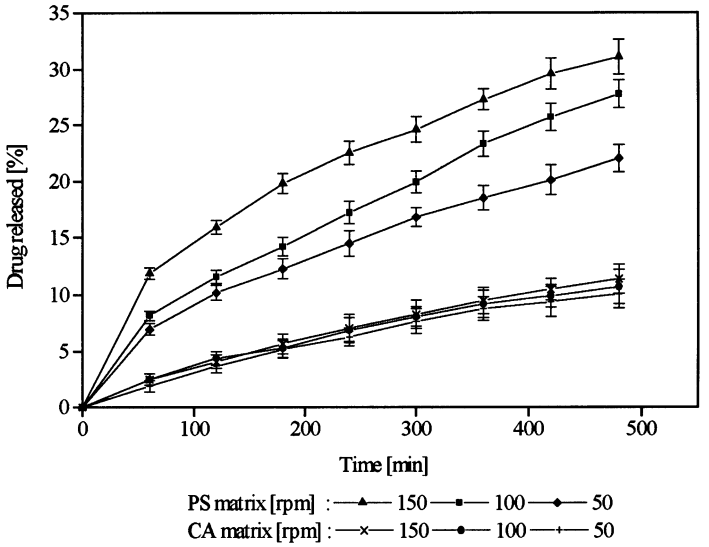

Fig. 4. Drug release from HPMC embeddings at different stirring speeds.

mer and a 400-mg portion of the mixture was filled in a brass cylinder with a 11.1-mm diameter and a height of 5 mm. The compression was accomplished with flat punches on a KP 2 single punch tabletting machine (Nagema, Wittenberg, Germany) where the lower punch was replaced by a special cup holder. Compaction pressure of 3 kN was equivalent to a crushing strength of nearly 65 ± 2 N (Erweka strength tester, Heusenstamm, Germany).

The cups were placed in a paddle apparatus (USP XXIII) with a rotation speed of 0, 50, 100 and 150 rpm respectively. Distilled water (500 ml) was used as dissolution medium and maintained at 37°C. Drug concentrations were continuously assayed by spectrophotometry. Front advancement was measured with a modified Höppler consistometer (Prüfgeräte-Werk Medingen, Germany) which was calibrated at 0.01 mm with a 0.5-mm diameter pin. The original steel rod was replaced by a PVC rod in order to minimize the strength leaning on the tablet surface. During the release test the system was withdrawn from the dissolution vessel and placed under the penetrometer pin at regular intervals of 1 h. The pin was moved down until the contact point with the outer part of the gelled layer could be measured (this point is the eroding front). In the next step, the pin was dipped into the swollen gel until the movement was stopped. At this point the glassy core was reached (swelling front).

2.2.2. System preparation and front advancement measurement with an ultrasound method

The mixture of HPMC and model drug was fed into the die of a rotary tablet machine (Pharmapress 100, Fa. Korsch, Germany) to produce a matrix tablet of 400 mg using flat punches. Compaction pressure was equal to preparation for penetrometer measurements.

For the ultrasound measurements the setup shown in Fig. 2 was used. The tablet adhered to the bottom of a plastic cylinder with a 11-mm diameter which was fitted to the top side of a PMMA tank (size: 10 cm × 12 cm × 8 cm). On the bottom of the tank an ultrasound transducer (PANAMETRICS V 311, 10 MHz) was positioned in a distance of 8 cm from the tablet. The tank was filled with distilled and degassed water. Ultrasound pulses were generated by the sender/receiver system DONOSON 2 (MINHORST). Changes in the acoustic impedance along the direction of ultrasound result in echoes reflected back to the transducer. Using a time gate the parts of the backscattered signals coming from the tablet were stored in a digital storage oscilloscope

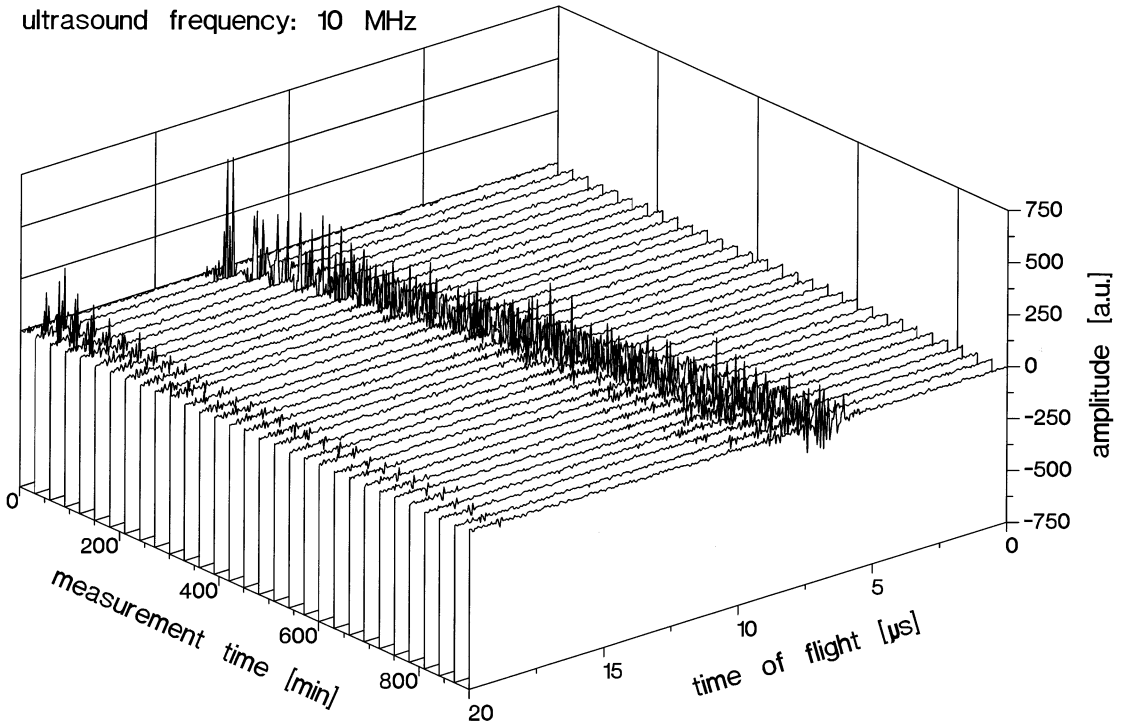

Fig. 5. Increasing thickness of gel layer during a period of 16 h in matrices with pholedrine sulphate.

(PM 3320, PHILIPS). After data transfer to PC via IEEE488-Bus the evaluations were done with the program DIA/DAGO (GfS Aachen). The time shift of peaks coming from eroding front was determined from the envelope of the radiofrequency signals. If the speed of sound c is known, the distance Δl between two reflecting structures could be determined from the difference of the times of flight Δt of their respective echos, that is:

$$c = \frac{2\,\Delta l}{\Delta t} \quad (1)$$

Measurements for the HPMC showed that the value for water ($c \sim 1500$ m/s at 25°C) is a good approximation for the gel as well.

3. Results and discussion

3.1. Kinetics of the eroding and swelling front

The advancement of the eroding front of matrices with pholedrine sulphate was greater than that of matrices with chloramphenicol and matrices without drug, respectively. This is demonstrated for a paddle speed of 50 rpm in Fig. 3. The zero position at the Y-axis is equivalent to the initial matrix surface.

The positions of the swelling front were not significantly different in all hydrodynamic conditions. The swelling and the eroding front advanced with an approximate constant velocity after 1 and 2 h, respectively. In each case, an increase of the gel layer thickness was noticed during the period of attempts. Although the velocity of the paddle increased, the two fronts advanced, whereas, the distance between them decreased. An increase in paddle rotation velocity lead to a decrease in the rate of advance of the eroding front, at which the rate of the swelling front increased. Table 1 shows this relation for matrices with pholedrine sulphate.

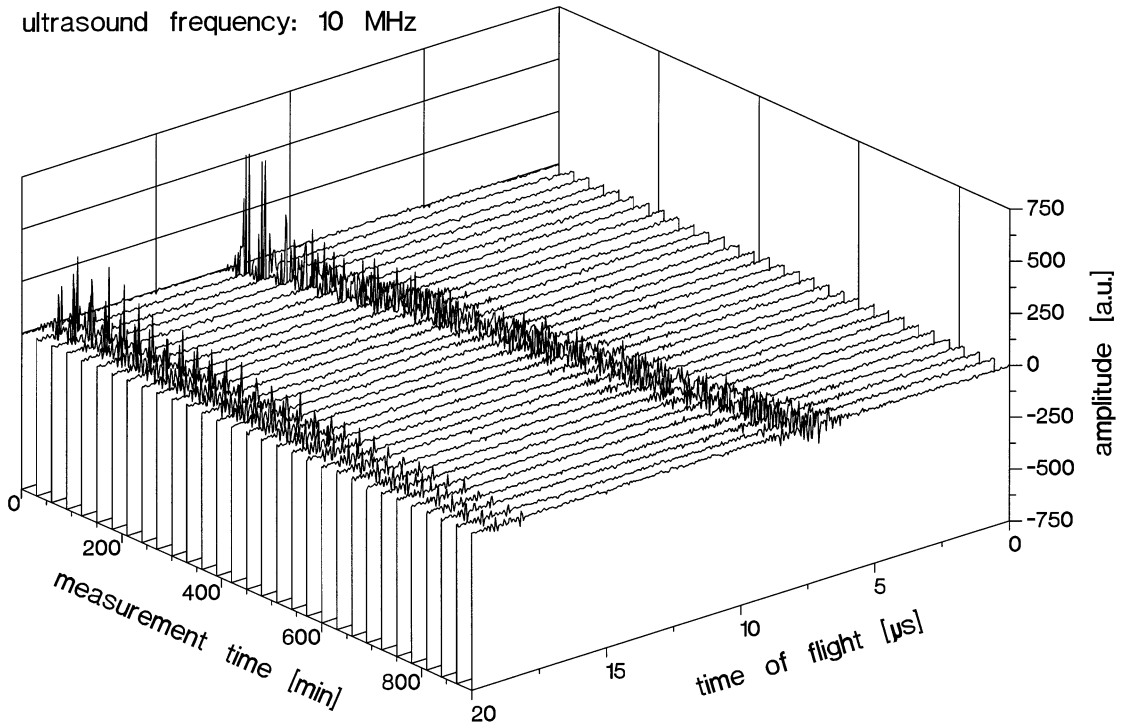

Fig. 6. Increasing thickness of gel layer during a period of 16 h in matrices with chloramphenicol.

The advancement of swelling and eroding front reduced with increasing hydrodynamic conditions certainly is true for both matrices with the same difference between 0 and 150 rpm.

A reduction in gel layer thickness at increasing stirring speed results in an increase of drug release. Matrices with pholedrine sulphate showed this behavior, whereas matrices with chloramphenicol did not (Fig. 4).

At the beginning of the release of pholedrine sulphate the rapidly dissolving drug on the surface produces a burst-effect. The constant drug release after 1 h could be a sign of a front synchronisation between eroding and diffusion front. In these case an increase in paddle rotation velocity would lead to a reduction of the distance between these two fronts (i.e. the thickness of the emptying zone) and therefore, to an increase in the release rate. This indicates that for a freely soluble drug a maximum of drug release or a minimum of gel layer thickness can be attained using a very high stirring speed.

In the case of pholedrine sulphate the diffusion in the dissolution medium is faster than that of the dissolved polymer, which dissolves only after a complete hydration of this polymer and the consequence must be a drug concentration gradient in the gel layer (Lindner et al., 1996).

The existence of a zero-order release rate from the start of release in the case of chloramphenicol can only be explained by assuming that the polymer dissolution determines the rate of drug release. Based on the low solubility of chloramphenicol the drug release is a passive consequence of polymer dissolution (Möckel, 1989). On these premises the velocities of eroding and diffusion front must be similar from the start, so that the thickness of the zone between diffusion and eroding front is constant over time.

Accordingly, the solubility of the drug and also the front position in the gel zone (particularly the diffusion front) played an important role as a rate determined step of drug release from this matrices.

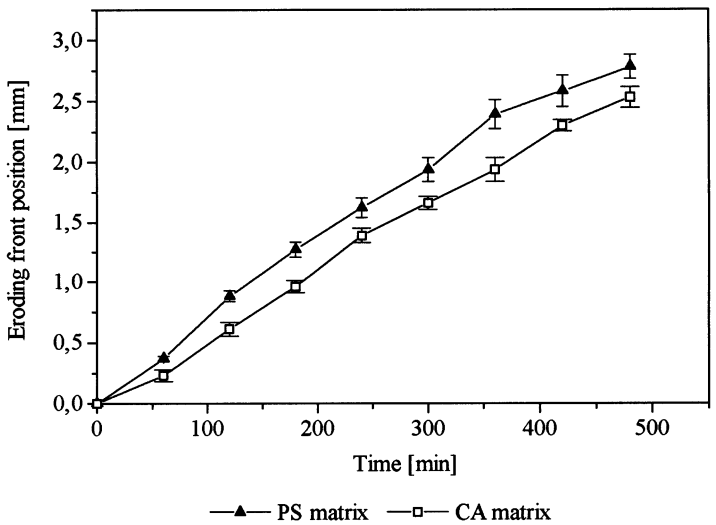

Fig. 7. Advancement of the eroding front position in HPMC matrices by ultrasound measurement over a period of 8 h.

3.2. Measurement of the thickness of the gel layer by an ultrasound method

Figs. 5 and 6 show that the ultrasound backscatter signals in matrices with pholedrine sulphate and chloramphenicol are dependent on the duration from the start of the experiment. Increasing values at the time of flight axis correspond after Eq. (1) to an increasing distance between the ultrasound transducer and the place where reflection back to the transducer occurs. The peaks at time of flight at about 20 μs correspond to the cylinder on the top side of the tablet. The start of the time gate was set to 0 μs, because only relative advancements are of interest. The difference between the 20 μs peaks and the peaks at about 12 μs at the beginning of the measurement (0 min) determines the thickness of the dry tablet. The high amplitude of the latter peaks is due to air included in the matrix during the tablet production, which results in a strong reflection of ultrasound at the tablet surface. The advancement of the outer border of the gel layer (eroding front) leads to a shift of these peaks into the direction of the transducer. Due to the permanent increase of water content in the gel layer and the gradual dissolution, respectively, the signals at increasing measurement time are more flat and the transition zone from water to gel becomes indistinct. General problems during ultrasound measurements result from major changes in acoustic impedance as these between water and air. This is not only true for the strong signals at the beginning of the experiments but also for air bubbles imbedded in the gel which lead to partially raised signals.

Fig. 7 illustrates the shifting of eroding front within 8 h.

The eroding front of matrices with pholedrine sulphate advanced faster than for matrices with chloramphenicol. This is in agreement with the results from the examination of the dynamics of the fronts by the penetrometer method. Table 2 shows the velocities of movement of the eroding front determined with penetrometer and ultrasound method, respectively.

The values indicate that with both methods nearly the same result is achieved. The advantage of the ultrasound method is the likelihood of continuous measurements, whereas for penetrometer measurements the tablet has to be removed from the system.

Table 2
Velocity of eroding front movement in HPMC matrices determined by penetrometer and ultrasound method

Method	Matrix with	Velocity of eroding front movement (mm/min)	s (%)	r
Penetrometer	PS	6.042×10^{-3}	5.59	0.993
	CA	5.353×10^{-3}	5.92	0.997
Ultrasound	PS	5.955×10^{-3}	4.22	0.994
	CA	5.468×10^{-3}	2.32	0.998

4. Conclusion

The dynamics of swelling and eroding front in HPMC matrices with freely and poorly soluble drugs were examined with the penetrometer method. Both fronts advanced over the time with different velocities. An increase in paddle rotation speed leads to a reduction of the distance between the two fronts. In the case of freely soluble pholedrine sulphate the drug release depends on the hydrodynamic conditions which is not the case for the poorly soluble chloramphenicol. Therefore the front positions in the gel layer and the solubility of drug influence the drug release. Accordingly, the diffusion of the drug through the gel layer should be taken into consideration as a rate determing step of the liberation process from this matrix.

A new method for characterizing the movement of eroding front has been described. A permanent measurement of advancement of eroding front and gel layer thickness without the removal of the tablet from the dissolving medium is possible when using backscattered ultrasound. Both methods achieved nearly the same result.

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