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Review Article

Advanced technologies for assessment of polymer swelling and erosion behaviors in pharmaceutical aspect

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ABSTRACT

Clearly understanding of swelling kinetics and erosion behavior of polymer can reveal drug release mechanism and kinetics. Recently, swelling progression and mobility of water molecule inside polymers have been investigated by several technologies, including magnetic resonance imaging (MRI), X-ray microtomography (XμT), Fourier transform infrared spectroscopy (FTIR), atomic force microscopy (AFM), fluorescent, texture analyzer, and ultrasound techniques. Each technique offers its own advantages which suit to different study purposes. This review describes application of the advanced technologies to monitor swelling–erosion behaviors and also compares pros and cons of each technique. This may help the researchers to select the appropriate technique for their polymer.

1. Introduction

Swelling and erosion of pure polymers or drug-polymer matrices in dissolution test media have been reported according to significant effects on ordinary dosage forms and controlled drug release systems [1–5]. The swelling properties may be altered in different media and by the ratio of polymer. High swelling progress with low erosion rate causes thick swelling gel layer or long diffusion distance for drug. Besides, strength of gel layer also affects diffusion coefficient of drug; thus, it can be said that the release kinetics of drug loaded highly depends on the swelling kinetics [6].

Although swelling properties of polymers were investigated by many techniques such as gravimetric technique (weight difference between dry and wet polymer) and optical observation technique (expansion area of gel layer of tablet fixing by Plexiglas®), some limitations have been observed, for example, the interference during weighing and error from removing excess solvent from the samples in gravimetric technique or the measurement of swollen gel under constrained condition in optical observation techniques [2,4,5,7]. According to the limitations of the conventional techniques, several advanced methods have been developed and applied to investigate the swelling and erosion behaviors of pure polymer and pharmaceutical dosage form. The aims of development are mainly to monitor swelling progress in real-time, simulate swelling condition to physiological condition, enhance ability to monitor swelling of small dosage form, and increase measurement precision of swelling and glassy regions.

Generally, purpose of most advanced techniques used is not for monitoring of polymer swelling but researchers accommodate application of equipment and use their outstanding points to improve the drawbacks of the conventional techniques and enhance swelling investigation efficiency. For example, MRI has been known as a medical imaging technique used in radiology to visualize detailed internal structures inside the body. However, it has been applied to monitor gradient of water molecule in hydrophilic polymer and controlled drug release systems [8,9] due to its ability to detect ^{1}H atom in water molecule. Another example is X-ray technique, which has been used for medical imaging. To observe swelling progress, X-ray has been used to monitor the movements of tracer particles embedded in the gel-forming tablet. Swelling and gel formation can be revealed by the movements of tracers that started close to the tablet surfaces [10].

This review attempts to give an overview on mechanism and application of the different advanced technologies which have been applied to examine swelling behavior of polymer related to drug release profile, that is, magnetic resonance imaging (MRI), X-ray microtomography (XμT), Fourier transform infrared spectroscopy (FTIR), atomic force microscopy (AFM), fluorescent, texture analyzer, and ultrasound techniques. Special attention is paid to the pros and cons of various techniques.

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2. Magnetic resonance imaging (MRI)

In the last decade, MRI, nuclear magnetic resonance imaging (NMRI), or magnetic resonance tomography (MRT) has been increasingly applied in pharmaceutical technology field for various purposes, for example, to monitor tumor-targeted polymeric micelles [11], to characterize push-pull osmotic controlled release systems [12], to visualize paramagnetic pH-triggered release liposomes [13], to monitor swelling behavior of the chitosan acetate matrix tablet, and to reveal drug release kinetics [8], etc.

2.1. Principle of MRI

Each water molecule has two hydrogen nuclei or protons, which can be typically observed by MRI. The MRI process starts with aligning of protons by the direction of electromagnetic field. Then, a radio frequency transmitter is briefly turned on, producing a varying electromagnetic field. If orthogonal magnetic field gradients are applied across the uniform static magnetic field during NMR acquisition, it is possible to spatially encode the signal in three dimensions. The signal intensity of a spin-echo image is dependent on the ^{1}H density, which is related to water concentration as well as the spin–lattice relaxation (T_1) and spin–spin relaxation (T_2) values, which are related to water mobility [14]. T_1/T_2 contrast images were used to highlight various features related to their water concentration and water mobility.

2.2. Advantages and application of MRI to monitor swelling profile

Among the several swelling observation techniques, MRI technique offers outstanding advantages since it is a real-time *in situ* monitoring without invasive and constrained condition [15]. Furthermore, MRI provides cross-sectional images from inside solid materials; therefore, it works well with complicated oral control drug delivery systems such as push–pull osmotic controlled release system and coated floating tablets [12,16]. MRI can also achieve full three-dimensional (3D) spatial resolution using orthogonal pulsed magnetic field gradients [17].

MRI was utilized to monitor swelling behavior of the compressed tablets of chitosan acetate (CSA) (Fig. 1) in order to reveal effect of chitosan molecular weight and pH of dissolution medium on drug release behavior. The swelling profiles were fitted with drug release patterns, and their correlation was evaluated. The swelling progress and erosion rate were significantly different in each medium. The swelling kinetics of CSA in pH 5.0 and pH 6.8Tris–HCl buffers were Fickian diffusion while that of 0.1 N HCl (pH 1.2) was close to zero order. The relationship between percentage of swelling and cumulative drug release was linear. The slope of the linear line indicates drug release mechanism [18]. If the slope is less than 1, the drug release from the matrix tablet should be diffusion mechanism. This is because more percentage of swelling the less drug release fraction.

High molecular weight CSA did not swell in pH 6.8 buffer but disintegrated into fractions, resulting in fast drug release [8].

3. X-ray microtomography (XμT)

XμT or computerized tomography scan is an advanced imaging technique, which can generate a 3D map of the specimen without destroying the original model. In the process, a series of X-ray images in different directions are used for reconstruction an image by assistance of computing technology. XμT have been developed for about 30 years, and in the 1980s, bench-scale XμT has been invented with a better resolution, micrometer scale [19].

3.1. Principle of XμT

Generally, the imaging contrast in XμT arises from different X-ray absorbances, which increase with the atomic number and mass density of the material. As reported by Roessl and coworkers [20], there are many factors to concern for obtaining X-ray image with high signal to noise ratio, for example, X-ray tube voltage, object diameter, and atomic number. They mentioned that the minimum difference of atomic number providing contrast in X-ray image is not certainly indicated. From the article, however, it can be generally concluded that if the X-ray operating parameters are optimally set, and the size of object is large enough, the difference of atomic number more than 10 can provide image contrast with high signal to noise ratio [20].

Moreover, XμT offer outstanding sensitivity in terms of density difference. The differences between physical material densities by less than 1% can be distinguished by XμT technique. Laity and Cameron [10] studied the swelling of hydroxypropyl methylcellulose (HMPC) tablet (relative density of 0.87–0.94) in distilled water by using XμT. The projected XμT images were collected (for example, Fig. 2). Contrast of the XμT images was sufficient to monitor swelling and expansion of the tablets [10]. Therefore, XμT is beneficial for examining cracks and voids within homogeneous materials or regions of different elemental compositions. However, to monitor swelling progress of polymer which mostly is organic compound, the high atomic number tracer is necessary for XμT. The imaging principle of XμT differs from MRI which detects gradient of ^{1}H from water. XμT has capability to provide 3D map of sample because XμT scanners offer isotropic, or near isotropic, resolution, display of images does not need to be restricted to the conventional axial images. Consequently, it is possible for a software program to build a volume by stacking the individual slice one on top of the other. The program may then display the volume in an alternative manner also.

3.2. Advantage and application of XμT to monitor swelling profile

XμT shows some privileges over MRI because MRI requires a sufficient water concentration within the material to lengthen the relaxation times associated with the nuclear spin magnetization and provide an observable echo signal above any background noise [15,21]. XμT method is able to show the movements within the relatively dry interior of the tablet. This reveals a clearly mechanical relaxation in the axial direction, within the tablet interior, ahead of the advancing hydration fronts that marked the (inward moving) limit of the MRI signal [22].

XμT has been extensively used in diversified fields of study including pharmaceutical area [23,24]. Laity and Cameron [10] used synchrotron XμT to determine swelling progress of the HMPC tablets by monitoring of movements of embedded glass microsphere tracers (Fig. 2). Then, swelling and dissolution profiles were analyzed. They also compared two advanced swelling investigation techniques, that is, MRI and XμT [22]. They reported that MRI provides information concerning the movement of hydration fronts into the tablets and the composition of the swollen gel layer. On the other hand, XμT explores axial expansion within the tablet core, at short times and ahead of the hydration fronts. Therefore, they recommended using MRI and XμT together for studying the hydration and swelling behavior of tablets.

4. Atomic force microscopy (AFM)

AFM or scanning force microscopy (SFM) is a surface investigation technique, which is one of the scanning probe microscopy (SPM), with demonstrated resolution on the order of fractions of

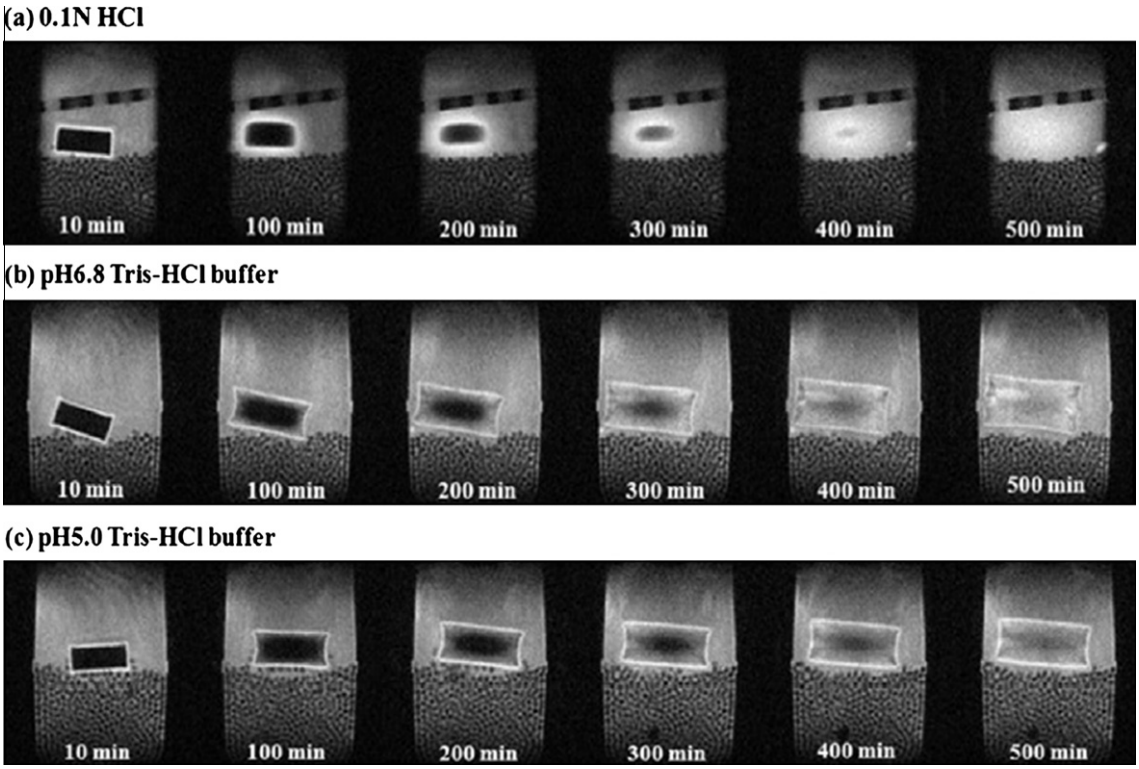

Fig. 1. MRI images of swollen CSA tablets prepared from 45 kDa chitosan in various media: (a) 0.1 N HCl, (b) pH 6.8, and (c) pH 5.0 Tris–HCl buffers [8].

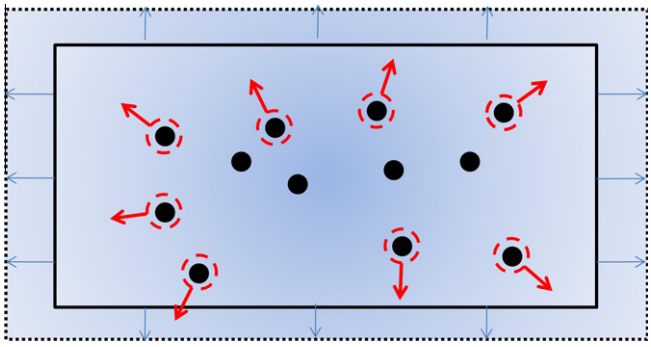

Fig. 2. Schematic of glass microsphere tracers (black dots) movement during swelling for HPMC specimen (arrows indicate direction of upward movement of the glass microspheres) [10]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

a nanometer, more than 1000 times better than the optical diffraction limit. AFM is particularly useful in elucidating fundamental aspects of the swelling in nanometer-scale of polymers in water and organic solvents, such as the influence of both solvent affinity and cross-link density on the swelling behavior [25].

4.1. Principle of AFM

AFM provides a 3D profile of the surface on a nanometer-scale, by measuring forces between sample surface and a sharp probe (less than 10 nm) at very short distance (0.2–10 nm). The probe micro-fabricated from Si or Si_3N_4 is supported on a flexible cantilever. To image the surface, the AFM tip gently touches the surface and records the small force between the probe and the surface. Nowadays, most AFMs use a laser beam deflection system, where a laser is reflected from the back of the reflective AFM lever and onto a position-sensitive detector. The force is not measured directly, but calculated by measuring the deflection of the lever, and knowing the stiffness of the cantilever; then, the image is generated from a difference of force.

4.2. Advantage and application of AFM to monitor swelling profile

The outstanding property of AFM is to examine swelling or cross-linking process of very small sample such as DNA and a single molecule of polymer. In pharmaceutical application, AFM was utilized to investigate swelling property and structure of modified surface polymer. For example, Paredes et al. [26] used AFM to monitor swelling of the poly(p-phenyleneterephthalamide) real-time, before and after modification by oxygen plasma treatment.

Another example is using the swelling data obtained from single xanthan molecules and films with AFM as a tool to predict swelling behavior and dissolution rate of xanthan matrix tablets in media of various pHs and ionic strengths [27]. The researchers found that microscopic polymer properties such as radius of gyration and persistence length are responsible for the macroscopic polymer behavior. For example, longer persistence length and radius of gyration of xanthan chains result in a higher degree of swelling, corresponding to softer polymer films, increased gel layers in matrix and a slower release rate of the incorporated drug from the tablets.

5. Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy

ATR-FTIR is a tool that has been proven to be useful in various applications. This technique is able to probe *in situ* single or multiple layers of adsorbed/deposited species at a solid/liquid interface. It is for this reason that ATR-FTIR has been implemented in various different biological and chemical studies in order to probe chemical reactions/structure at the solid/liquid interface. In polymer science studies, ATR-FTIR spectroscopy is finding increased use as a

tool to study the sorption and transport of penetrants in polymers. From this principle, there have been some studies that used the unique capability of ATR-FTIR spectroscopy to study penetrant-induced polymer swelling.

5.1. Principle of ATR-FTIR

ATR generally allows qualitative or quantitative analysis of samples with little or no sample preparation, which greatly speeds sample analysis. The principle of ATR-FTIR is to use a property of total internal reflection, resulting in an evanescent wave. As shown in Fig. 3, a beam of infrared light is passed through the ATR crystal in such a way that it reflects at least once off the internal surface in contact with the sample. This reflection forms the evanescent wave which extends into the sample. The penetration depth into the sample is typically between 0.5 and 2 μm. Therefore, the main advantage of ATR sampling comes from a very thin sampling path-length and depth of penetration of the IR beam into the sample. This is in contrast to traditional FTIR sampling by transmission where the sample must be diluted with IR transparent salt, pressed into a pellet or pressed to a thin film, prior to analysis to prevent totally absorbing bands in the infrared spectrum [28].

ATR-FTIR spectroscopy has been applied to *in situ* monitor polymer swelling and diffusion process by analysis tracking of a given penetrant polymer system using IR spectra.

As illustrated in Fig. 3, penetrant from top of the polymer membrane diffused into the glassy polymer layer, resulting in a gradual increased portion of penetrant in the polymer. Increment of penetrant is quantitatively *in situ* detected via ATR-FTIR spectra. Then, the obtained spectra (e.g., intensity of the peak(s) in the spectra, as shown in Fig. 4), are interpreted to quantitative data. Finally, the rate of penetrant diffusion in the polymeric matrix and the relaxation rate of the polymer chains during sorption are revealed.

5.2. Advantage and application of ATR-FTIR to monitor swelling profile

During the last decade, ATR-FTIR technique has been applied to examine polymer swelling or dilation in field of polymer science and pharmaceutics. The application of the ATR-FTIR technique for the study of polymer-penetrant systems allows for the determination of the transport properties of the penetrant from IR absorbance peaks associated with the penetrant and can also offer information on polymer swelling through changes in the IR absorbance peaks of the polymer. Baschetti and coworkers [29]studied the polymer swelling and penetrant sorption kinetics of three different polymers, that is, polycarbonate, poly(vinyl acetate), and poly(ether urethane), induced by the sorption of vapor phase acetonitrile. The swelling of the polymers was monitored through carbonyl (C=O) group stretching band. When the polymer swells during penetrant sorption, the concentration of polymer chains

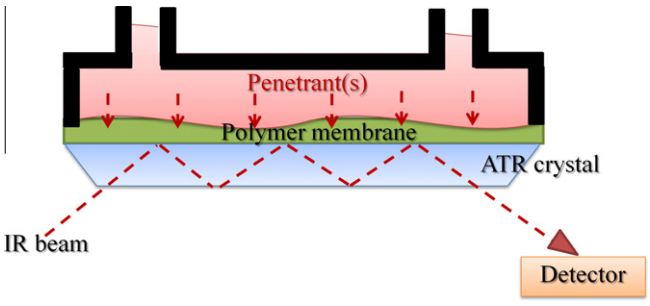

Fig. 3. Working process diagram of ATR-FTIR. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

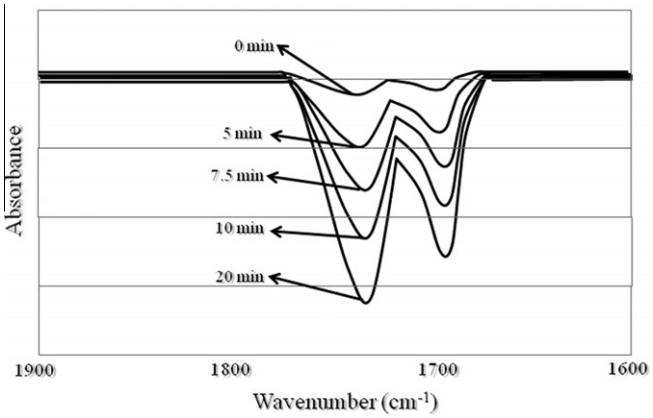

Fig. 4. IR absorbance of polymer characteristic peaks (poly(vinyl acetate)) during acetonitrile diffusion in different time points [29].

in the region probed by the infrared beam decreased, lowering the number of polymer functional groups that can interact with the IR beam and absorb energy. Decline in the integrated absorbance of the polymer peaks is a result of such the process and can be used to evaluate the matrix volume change upon mixing (Fig. 4). The polymer swelling data from ATR-FTIR were compared with those of volume change measurements monitored by CCD camera. The result expressed excellent agreement between the two techniques [29].

Guo and Barbari [30] used ATR-FTIR spectroscopy to study the swelling of cellulose acetate induced by the sorption of vapor phase acetonitrile. The result reveal that the unified dual mode model (penetrant sorption and desorption kinetics) can predict ATR-FTIR swelling kinetics. Furthermore, the IR absorbance data for swelling at equilibrium were found to be in excellent agreement with those from direct measurements [30].

All the examples show the advantages of using ATR-FTIR to investigate polymer swelling which bestow the information regarding to behavior of penetrant movement and effect of dissolution medium on chemical structure of polymer. In addition, this technique is nondestructive method, and real-time swelling progress monitoring is possible. Consequently, the ATR-FTIR method is a good alternative for studying polymer swelling *in situ*. However, this technique is not direct measurement of polymer volume. Therefore, swelling region, glassy region, swelling front, and erosion front are not obtained from this technique. Moreover, the prediction ability of swelling progress from ATR-FTIR might not work well with all kinds of polymer and swelling kinetics.

6. Fluorescence

Fluorescence techniques have been introduced to swelling polymer study since last decade. This is because various fluorescence techniques, such as steady-state spectroscopy, fluorescence anisotropy, and fluorescence decay measurements are potential tools for studying of molecular diffusion or molecular interaction with high sensitivity [31].

6.1. Principle of fluorescence

This method is basically based on the detection of excited fluorescent molecules desorbing from a polymer (solid state) into gel or solution forms [32]. In dry condition, chromophores of fluorescent molecules are in steady state, until molecules of water or solvent diffuse into polymer causing swelling progress. The interactions between the chromophore and the solvent molecules affect

the energy difference between the ground and the excited states. This energy difference is called the Stokes shift depended on the refractive index and dielectric constant of the solvent. By measuring the Stokes shift of a polarity sensitive fluorescent species, swelling progress can be monitored.

6.2. Advantage and application of fluorescence to monitor swelling profile

Fluorescence techniques have been vastly utilized in many areas such as pharmaceutics, biomedicine, biology, and material sciences. This is because fluorescence techniques provide high sensitivity and versatile result, and the instruments are commercially available [33]. Fluorescence dyes have been used in two basic types of experiments. First, by simply addition of dye to a system as a small molecule, the dye is referred to as a probe. Secondly, fluorescent molecules are covalently attached to a system, such as a polymer chain. Then, fluorescent molecules are monitored as referred label.

Erdoğan and coworkers [31] conducted the *in situ* steady-state fluorescence experiments by using pyrene as a labeling agent. This study was performed for studying swelling behavior and slow release of polystyrene polymer by attaching pyrene into polystyrene chain. Pekcan et al. [34] also monitored pyrene fluorescence intensity to investigate the swelling process in gels formed by free radical cross-linking copolymerization of methyl methacrylate and ethylene glycol dimethacrylate. Pyranine is another fluorescent dye which has been employed as a marker to examine swelling kinetics. Tari and Pekcan [35] embed pyranine in carrageenan in dry state to investigate the effect of temperature and polymer concentration on swelling progress of the polymer in water vapor.

7. Texture analysis

Texture analysis is a physical investigation technique, which has been applied to monitor swelling behavior of several hydrophilic polymers [36–38]. This technique has been consecutively developed to overcome its previous drawbacks such as sample destruction and non-real-time monitoring [3]. The developed texture analyzer offers useful information such as the swelling and erosion rates, rubbery, and glassy regions. Moreover, this technique also provides the strength of swollen gel, which is crucial data to predict and explain drug release kinetics.

7.1. Principle of texture analysis

Generally, the principle of a texture analysis in swelling investigation application is to deform a swollen polymer in a controlled manner and measure its response force from swollen gel and glassy core. In experiment, the swollen polymer in tablet form is removed from dissolution medium at a given time interval. Then, the thickness of the swollen gel layer, glassy core, gel, and glassy core stretches are measured by a penetration probe fitted to a texture analyzer [39]. However, this technique has been developed due to lack of real-time monitoring and actual gel structure in dissolution medium environment. The force detector probe of the texture analyzer was modified, as shown in Fig. 5. From the novel probe, thickness of gel region and erosion rate can be *in situ* examined in dissolution medium [3]. Moreover, the gel layer formation and its dynamics as a function of time can be evaluated by texture profiling analysis [5].

7.2. Advantage and application of texture analysis to monitor swelling profile

The preference of gel texture analysis is information of gel strength, which is not obtained from the other techniques. Several

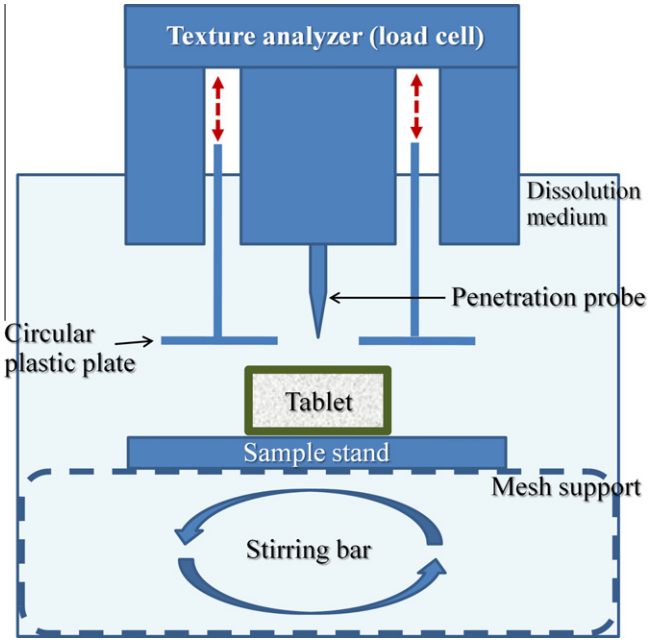

Fig. 5. Schematic representation of the experimental assembly and the novel probe [3]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

imaging techniques might propose of accurate gel swollen area, but gel strength and porosity are also crucial data affecting drug release rate and kinetics.

Ng and Swami [36] utilized texture analyzer to investigate relation between relative stress relaxation value and swelling kinetics of photo-polymerized 2-hydroxyethyl methacrylate/N-vinyl pyrrolidinone hydrogels in different ratios. Texture analysis denoted the existence of a trend between stress relaxation and diffusion kinetics of the hydrogels and the gels displayed non-Fickian diffusion have significantly lower stress relaxation values. Yang et al. [38] determined water penetration front of HPMC and polyethylene oxide (PEO) using texture analyzer. To examine gel layer thickness, sample was placed on the platform in stirred medium, and the probe travelled to the surface of the swollen gel which was detected. Then, the probe kept moving until reaching the dry core. The distance between gel surface to dry core was collected as a gel layer thickness. Sriamornsak et al. [5] reported the decreased elastic modulus of the swollen gel layer of various pectins when the swelling time increased. In this context, a high elastic modulus at the beginning of the tests is likely to provide erosion resistance to the hydrated layer whereas a highly swollen layer with a low elastic modulus is likely to be washed away more quickly by the dissolution medium.

8. Ultrasound technique

Ultrasound technique is the fundamental nondestructive method for investigation into materials and structures. A crucial part of ultrasonic inspection is the way in which the ultrasonic energy is transferred between the transducer and the tested object. This technique has been applied to detect gel front movement of hydrophilic polymer since it is not costly advanced technique and possible for routine measurements.

8.1. Principle of ultrasound technique

The principle of ultrasound is to discover a surface of two different density substances, which generally are between medium and

investigated polymer. In measurement process, ultrasonic pulses are generated by the sender/receiver system. Changes in the acoustic impedance along the direction of ultrasound cause echoes reflected back to the transducer. Using a time gate, the parts of the backscattered signals coming from the tablet are stored in a digital storage oscilloscope. Then, data are transferred and analyzed in a computer. The time shift of peaks coming from eroding front is determined from the envelope of the radiofrequency signals. If the speed of sound (c) is known, the distance between two reflecting structures (Δl) could be determined from the difference of the times of flight of their respective echos (Δt), that is [40]:

$$c = \frac{2\Delta l}{\Delta t}$$

8.2. Advantage and application of ultrasound technique to monitor swelling profile

The benefits of ultrasound technique are the nondestructive investigation and the possibility of continuous measurements with low budget investment. The ultrasound technique does not directly measure material density as X-ray does. The ultrasound technique, however, examines distance between sender/receiver and interface of two materials with different densities. In the application of swelling determination, two interfaces (i.e., erosion front and swelling front) in polymer swelling system are investigated. The interface between swelling medium and polymer gel is used as a mark to detect erosion front, while the interface between polymer gel and polymer glassy region is used to locate swelling front. Konrad and colleagues [40] are the first group who applied ultrasound in pharmaceutical field. They measured backscattered ultrasound signals to characterize advancement of eroding front of the HPMC matrix tablets. The swelling behavior result of the HPMC matrix tablets from ultrasound method was not different from that of the penetrometer. The correlation between drug release and swelling data was also observed.

Leskinen and coworkers [41] also developed ultrasound technique to explore movement of the eroding front belonging to HPMC and PEO tablets. The samples were placed in the holder made of a polymethylmetacrylate (PMMA, a transparent material) rod, as illustrated in Fig. 6. From the scheme, the hydrogel layers and the dry core of a swelling tablet can be detected as a function of scanning location. The result showed that the sensitivity to follow hydrogel formation and thickening by ultrasonic 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 micro bubbles formed inside the hydrogel were acting as a contrast agent, characteristic of some polymers during immersion.

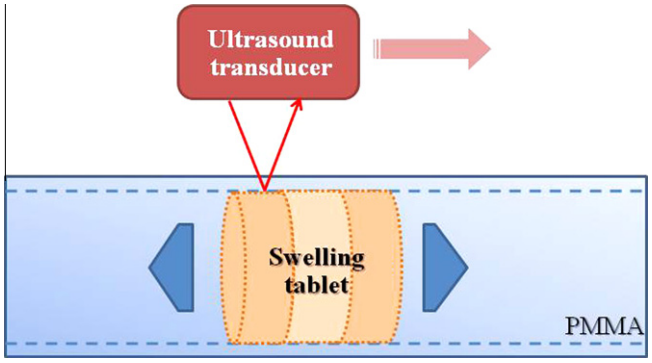

Fig. 6. A schematic illustration of the ultrasound window setup: ultrasound transducer scanning parallel to the axis of the sample tablet located in a transparent acrylic (PMMA) block acting as an ultrasonic window [41]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

9. Conclusions and future trend of swelling examination

Several advanced technologies have been applied to improve sensitivity and accuracy of result. Besides, the swelling study conditions have been simulated to human gastrointestinal condition to reveal swelling kinetics and drug release mechanism. The monitoring of swelling process tends to be real-time and noninvasive method in order to minimize swelling interference factors. Each investigation technique is suitable for different purposes of study.

The advanced swelling investigation techniques start to move from academic research to industrial section. This is because the usefulness of the obtained information can develop new advanced drug delivery system and also explains and solves the formulation problems in solid dosage forms. However, the expenditure of the technology is high. Consequently, the application of the new techniques is limited in affordable institute. Recently, several studies endeavor to rectify the investigation equipment from huge size to bench top scale and also reduce cost of research conduction. In the near future, the swelling properties of the pure polymer or solid dosage form will be generally investigated by the advanced technique, and more equipment will be available in the market.

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