European Journal of Pharmaceutics and Biopharmaceutics 74 (2010) 371–376

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

Scratch resistance of plasticized hydroxypropyl methylcellulose (HPMC) films intended for tablet coatings

Kalle Hanhijärvi [a,*], Terhi Majava [b], Ivan Kassamakov [c], Jyrki Heinämäki [b], Juha Aaltonen [d], Jonne Haapalainen [a], Edward Hæggström [a], Jouko Yliruusi [b]

[a] Department of Physics, University of Helsinki, Helsinki, Finland
[b] Division of Pharmaceutical Technology, University of Helsinki, Helsinki, Finland
[c] Department of Micro and Nanosciences, Helsinki University of Technology, Espoo, Finland
[d] Helsinki Institute of Physics, University of Helsinki, Helsinki, Finland

ARTICLE INFO

Article history:
Received 30 June 2009
Accepted in revised form 16 September 2009
Available online 22 September 2009

Keywords:
Film
Hydroxypropyl methylcellulose
Plasticizer
Scratch resistance
Scanning white light interferometry
Aging

ABSTRACT

Scratch resistance (SR) of externally plasticized hydroxypropyl methylcellulose (HPMC) films intended for tablet film coatings was studied. Special attention was paid to effects of short-term aging and ultraviolet (UV) treatment on the SR properties of these films. Controlled scratching of the films was performed with a Lloyd LRX materials tester featuring a spherical steel tip. Scratch surface profiles were measured by scanning white light interferometry (SWLI). The influence of using an external plasticizer on the SR was studied by comparing scratch dimensions in non-plasticized films to samples plasticized either with glycerol or polyethylene glycol (PEG) 400. The study demonstrates that both the amount and type of plasticizer influences the SR of aqueous HPMC films. It also shows that SWLI can quantitatively evaluate the effect of plasticizer content and aging on the SR of pharmaceutical films. This knowledge could be used to optimize pharmaceutical film coating formulations.

1. Introduction

Film coatings are extensively used in pharmaceutical manufacturing of solid dosage forms (i.e. tablets, granules, pellets and drug crystals). Hydroxypropyl methylcellulose (HPMC) is the most widely used cellulose polymer in pharmaceutical film coatings. These coatings mask the taste, odor or color of the drug in addition to providing physical and chemical protection for the drug. The scratch resistance (SR) of HPMC films can be improved with external plasticizers such as glycerol or low molecular weight polyethylene glycols (PEGs) [1–3].

Defects in tablet film coatings can significantly degrade the aesthetic appeal, performance, and shelf life of the drug product [4]. A material's resilience towards scratch deformation is described by its SR [5], which is derived from the material response. Despite improvements in film coating technology, problems still exist with long-term performance of polymer coatings exposed to hostile environments, e.g. humidity, temperature, acidity, and mechanical impacting [6–8]. Several tests can be used to evaluate coating performance. Contact tests efficiently rank materials with respect to their mechanical performance [9]. While indentation tests provide quantitative information about stiffness and elastic recovery of materials, SR tests provide qualitative information concerning failure mechanisms like initiation of rupture [10]. SR tests also differentiate ductile fractures from brittle ones [11]. Scratch dimensions, however, provide the base for quantitative methods that evaluate film aging and development [7]. To date, little work has been done on methods and techniques that can improve our understanding of scratch formation mechanisms and SR related to pharmaceutical tablet film coatings.

Scanning white light interferometry (SWLI) is a rapid non-contact, areal data capturing optical technique for surface characterization and scratch determination [12–16]. SWLI can, with proper magnification and suitable scan lengths, measure a large variety of grooves and dents without sample preparation. Only few reports exist on application of SWLI for polymer SR testing and characterization [14]. To our knowledge, no studies on scratch visibility in pharmaceutical tablet film coatings by using a non-contact SWLI technique have been reported.

Therefore, we set out to study scratch formation and resistance of externally plasticized hydroxypropyl methylcellulose films intended as conventional film coatings of tablets. We focused on cast films to limit the number of variables in the scratching process. For

* Corresponding author. Electronics Laboratory, Department of Physics, P.O. Box 64 (Gustaf Hällströmin katu 2a), University of Helsinki, FI-00014, Finland. Tel.: +358 9 19150695; fax: +358 9 19150694.
E-mail address: kalle.hanhijarvi@helsinki.fi (K. Hanhijärvi).

0939-6411/$ - see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2009.09.006

coated tablets, the hardness of the substrate influences the scratch formation [8]. Repeating the measurements for coated tablets is a subject of a future study. The effect of the plasticizer on the SR of the coating was chosen as our focus. This kind of study can be done by comparing non-plasticized films to the samples prepared with glycerol or PEG 400 as external plasticizers. After the influence of the plasticizer is established, one can further study the effects of a short-term ultraviolet (UV) treatment and aging at various storage conditions (i.e. humidity, temperature). The environmental conditioning study can be done with the involved films plasticized with glycerol. These cases provide a means to show that SWLI can be used as a novel non-invasive technique to determine the SR of pharmaceutical films.

The scratch hardness H_s was used to characterize SR [5,17]. H_s is defined as:

$$H_s = \frac{W}{A}, \quad (1)$$

where W is the normal scratching force, A is the projected contact area [5,17]. For a spherical tip, the contact area can be given in terms of scratch width:

$$A = \frac{\pi d^2}{4}. \quad (2)$$

The scratch hardness can be calculated from a linear fit to the (A, W) data set:

$$W = H_s \cdot A, \quad (3)$$

where H_s is given by the slope of the fit.

2. Materials and methods

2.1. Materials

Hydroxypropyl methylcellulose (HPMC) was used as a film former (Methocel E5, Colorcon Ltd., UK). Glycerol (Ph.Eur.) and polyethylene glycol, PEG 400 (Ph.Eur.) were studied as external plasticizers. Purified water was used as an aqueous solvent.

2.2. Sample preparation

Films were prepared separately for both experiments. The general procedure is similar, and the following description notes the differences where applicable. Since the samples were prepared in laboratory conditions, the relative humidity could be controlled neither during the initial preparation step nor during the measurement. For the final drying stage and long-term storage, the samples were placed in a vacuum desiccator to keep the humidity constant.

Customized Teflon (DuPont) molds were used for the film solution during the SR study. However, these films spontaneously detached from the molds due to delamination, becoming effectively free films. The SR study involved only measuring scratch widths with optical microscopy. This measurement was unaffected by the delaminations. Free films would not have worked for the relaxation study due to their uncontrolled deformation, hence these films were cast on glass plates. The films cast on glass plates exhibited only minor delamination.

The composition of the aqueous coating solution was HPMC 10% (w/w) as a film former and purified doubly distilled water as a solvent. In the SR study, the plasticizer was glycerol or PEG 400 in equal concentrations (30% w/w of the polymer weight). For the relaxation study, glycerol was used as a plasticizer (20% w/w). HPMC was dissolved into one third of the warm (T = 75 ± 5 °C) solvent. The remaining water was added, after which the solution was stirred for 1.5 h using a magnetic stirrer. Next, plasticizer was added, and the solution was stirred for 30 min. For the SR study, the solution was cast into customized Teflon molds (10.5 ml each). The films used for the relaxation study were cast on clean glass plates using a finnpipette (2 ml on each glass plate). Films were dried in laboratory conditions (23.0 ± 0.5 °C, 30 ± 5% relative humidity) for 24 h (relaxation samples) or 48 h (SR). The resulting film thickness was 90 ± 10 μm for the relaxation study samples. The SR sample thickness was 125 ± 5 μm, 175 ± 5 μm, or 170 ± 5 μm for films with no plasticizer, glycerol, or PEG 400, respectively. Finally, the films were stored for 4 days in a vacuum desiccator, with an over-saturated salt solution of K_2CO_3 generating a relative humidity (RH) of 43% at 23.0 ± 0.5 °C.

2.3. Scratching tests

Controlled film scratching was performed with a materials testing machine (Lloyd Instruments Ltd., UK) featuring a 1 mm diameter spherical steel tip and a 10-N load cell. The force applied during the SR study was 3.0 N, 4.0 N, and 5.0 N, whereas it was 3.0 N during the relaxation study (normal incidence). The scratching speed was 16 mm/min. At least three parallel scratches, spaced 15 mm apart, were made on each film. The scratching was done in laboratory conditions (23.0 ± 0.3 °C, RH 24 ± 5%). The scratching system and set-up for the films are shown in Fig. 1. Fig. 1C shows the scratch orientation on a prepared film.

Polymers exhibit viscoelastic behavior, which suggests that the tip speed affects the scratch formation process [5]. The materials testing machine limited the speed to a fixed value. This made speed comparison practically impossible to carry out. A thorough

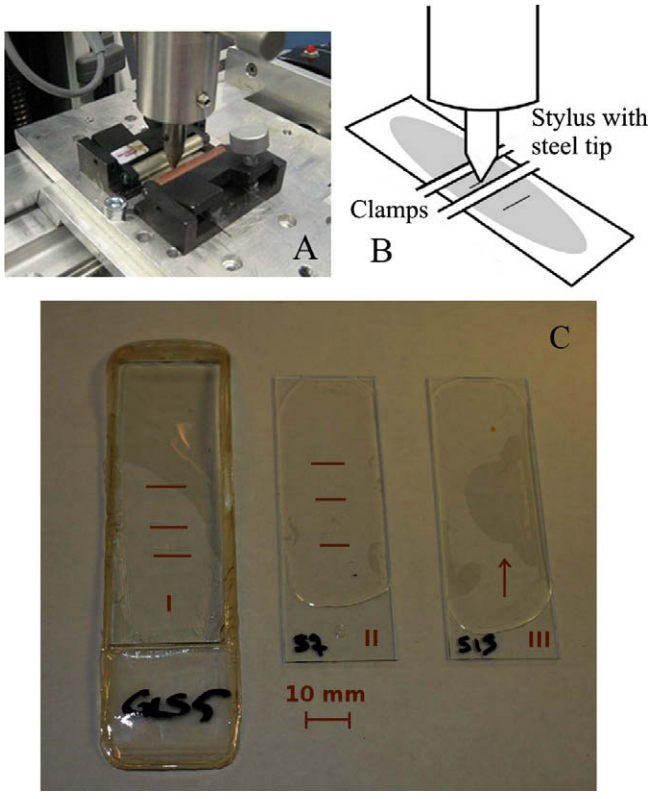

Fig. 1. (A) Controlled scratch test device and set-up. (B) Schematic of the scratching arrangement. (C) Photograph of scratched and conditioned films. Scratch positions are highlighted in the image. Film prepared in the Teflon mold (SR study, I). Films prepared on glass plates (relaxation study, II and III). The image was gamma corrected [18] with a factor of 0.25 to improve the visibility of delaminations (darker patch, indicated with an arrow). (For interpretation of color mentioned in this figure the reader is referred to the web version of the article.)

study of the effect of viscoelasticity of HPMC on scratch behavior is the subject of a future study.

2.4. The conditioning process

To emulate film aging, the samples were exposed to ultraviolet (UV) light and stored either at a high relative humidity (75% RH) at room temperature (23.0 ± 0.5 °C) or in 50 °C (oven). For reference, a set of film samples were stored in the high humidity conditions without UV treatment. No non-irradiated samples were stored at high temperature. The films were irradiated for 15 min with a light-emitting diode (LED, Hero HUVL370-510), featuring a 370 nm peak wavelength. The LED was driven in pulse mode at 120 Hz, with a duty cycle of 40% and current amplitude of 350 mA (0.2 mW/cm^2 illumination). The UV exposition of the film samples was performed using either (#1) pulsed LED UV irradiation, or (#2) 20 s high power irradiation with a standard UV pistol (UCL 300 Teklite high intensity UV curing unit, Electro-Lite Corporation, 320–420 nm), or (#3) 15 min irradiation with continuous UV irradiation from the LED (40 mA DC, 0.1 mW/cm^2 illumination). Some of the films experienced delaminations during the conditioning process (Fig. 1C). The defects were probably due to the combined effect of residual impurities on the glass plate and environmental conditioning.

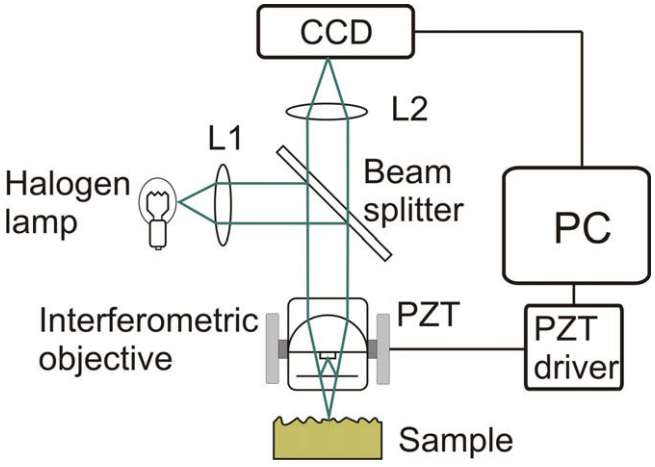

Fig. 2. Operational principle of a scanning white light interferometer. (For interpretation of color mentioned in this figure the reader is referred to the web version of the article.)

2.5. Scanning white light interferometry

Scratch profiles were measured with a scanning white light interferometer both prior to UV treatment and during a 4 weeks short-term aging test. In SWLI, a light beam passes through an interferometric objective (Nikon, Michelson type, magnification 5×) containing a beamsplitter that reflects half the incident beam to a reference surface and that passes the other half to the test surface (Fig. 2). Light reflected from the test and reference surfaces recombine and interfere, forming an interferogram. The objective is moved (scanning) and several interferograms are sequentially imaged. For each CCD camera pixel, the modulation signal is extracted from the intensity signal as the optical path difference is varied through the objective's focus. The peak of the modulation signal is detected, and a measurement of relative surface height at that point is produced. The modulation signal is inherently aperiodic for white light sources and is, therefore, not subject to the

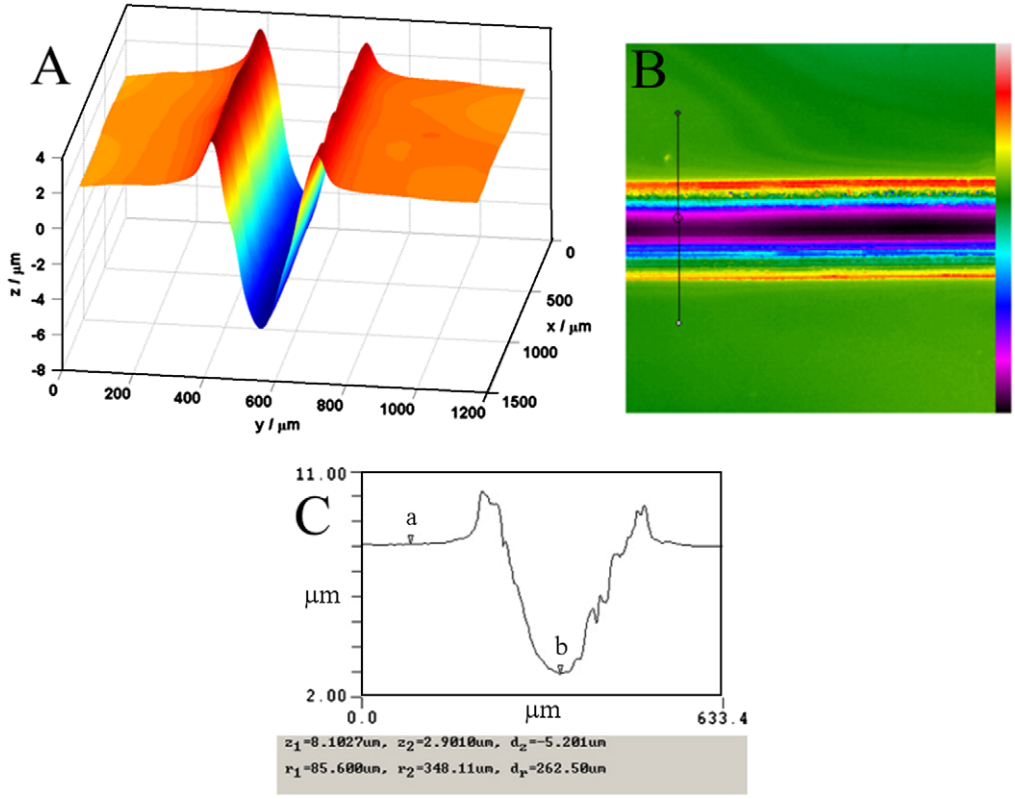

Fig. 3. (A) Typical scanning white light interferometry (SWLI) 3D image of a scratch used for depth measurement. (B) 2D image of the scratch. (C) The scratch depth measured from the flat film surface to the scratch floor served as a control parameter. The level of the unscratched surface (a) and the bottom of the scratch (b) are indicated. (For interpretation of color mentioned in this figure the reader is referred to the web version of the article.)

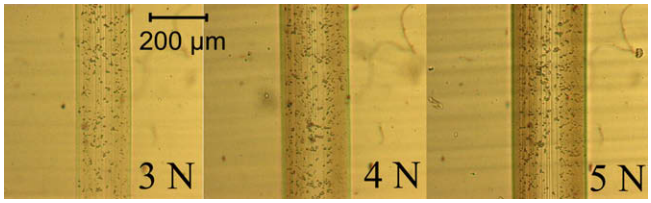

Fig. 4. Typical optical microscopy images of scratches in a non-plasticized aqueous HPMC film. Scratching (loading) forces were 3 N, 4 N, and 5 N. (For interpretation of color mentioned in this figure the reader is referred to the web version of the article.)

ambiguity problems that affect phase measurement methods. The technique can measure rough surfaces and steps up to several millimeters in height. The height data are calculated from the interference data with nanometer resolution. A typical SWLI 3D image of a controlled scratch used for depth measurement is shown in Fig. 3A. The scratch depth was defined to be the difference in height measured from the flat film surface to the scratch floor (Fig. 3B and C).

2.6. Optical microscopy

The width of the generated scratches was determined by optical microscopy (Leica DMLB, Leica Mikroskopie und Systeme GmbH, Germany, 5× magnification) equipped with an RGB charge-coupled device (CCD) camera (Sony XC-003P, K-Vision BV, the Netherlands, 752 × 582 px, pixel size 6.5 × 6.25 µm) and Leica QWin Runner program.

3. Results and discussion

Scratch visibility in polymers measured using optical imaging techniques has been reported [19]. Typical optical microscopy images of scratches seen in non-plasticized aqueous HPMC films are shown in Fig. 4. Increasing the normal scratching force (from 3 N to 5 N) increased the scratch width in non-plasticized HPMC films. Including a plasticizer (glycerol or PEG 400) made the films more sensitive to the scratching force and resulted in wider scratches compared to the corresponding non-plasticized films (Fig. 5). This finding is supported by previous studies where the loading force and the plasticizers similarly affected the scratch dimensions in polymer films [20–22].

The H_s values for both plasticized and non-plasticized HPMC films were calculated according to Eq. (3), Fig. 6. The scratch hardness value for non-plasticized HPMC films was 91.0 ± 11.0 MPa, while the values for the plasticized films were 34.0 ± 2.0 MPa (PEG 400) and 35.5 ± 2.0 MPa (glycerol), respectively. The errors are calculated from the uncertainty of the least-squares fit. Both the amount and type of plasticizer influenced the SR of aqueous HPMC films. This finding should be taken into account when developing formulations for the present tablet film coatings by optimizing the plasticizer content for maximum SR.

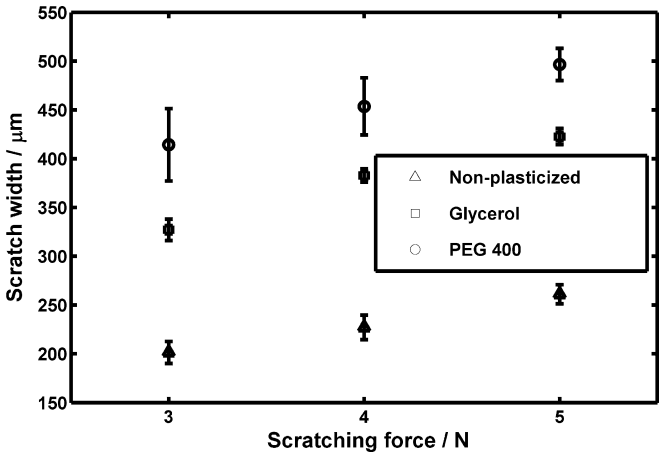

Fig. 5. Effects of scratching (loading) force and plasticizer on scratch width (n = 3). Error bars indicate the standard deviation from three measurements.

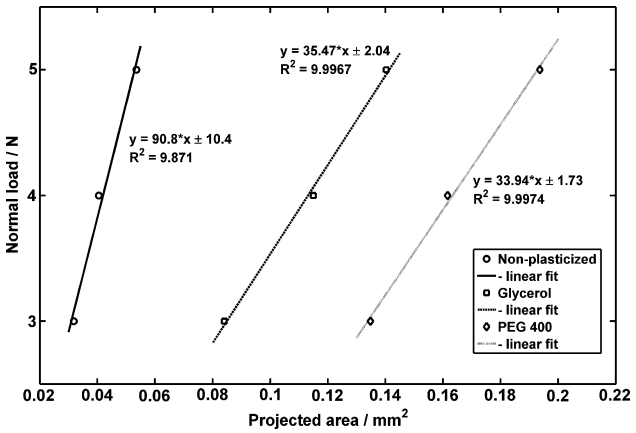

Fig. 6. The normal loading force (N) applied during scratching as a function of the contact surface area (mm^2) of the scratch.

The scratch depth measured with interferometry from the flat film surface to the scratch floor was used as a control parameter (see Fig. 3C for explanation). The scratch depth was normalized to the value obtained from the measurement before storage. Figs. 7–9 show the changes in scratch depth during short-term aging at different storage conditions. After the scratching process, viscoelastic polymer relaxation is likely to occur, the scratch eventually shallows [7]. According to Briscoe et al., the effect of viscoelastic relaxation on the scratch width is insignificant, rendering width an uninteresting parameter in the relaxation study [23]. Mean scratch depths and standard deviations before the conditioning are listed in Table 1.

Comparing the change in scratch depth for different samples as a function of storage time reveals a relationship between the relaxation and the nature of the pre-storage treatment (Figs. 7–9). Relaxation is defined as the relative decrease in scratch depth with

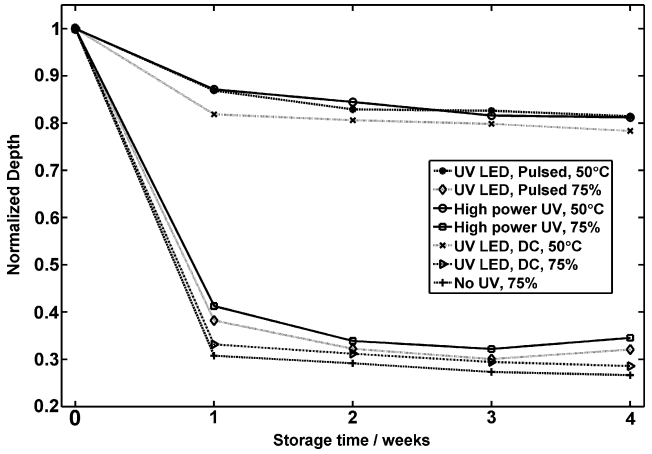

Fig. 7. Normalized scratch depth in HPMC films as a function of aging time and conditioning. Scratch depths are normalized averages for each treatment and storage condition. Standard deviation of measurement is 1–5%. A commercial UV pistol was used to irradiate the high power samples (see text for specifications).

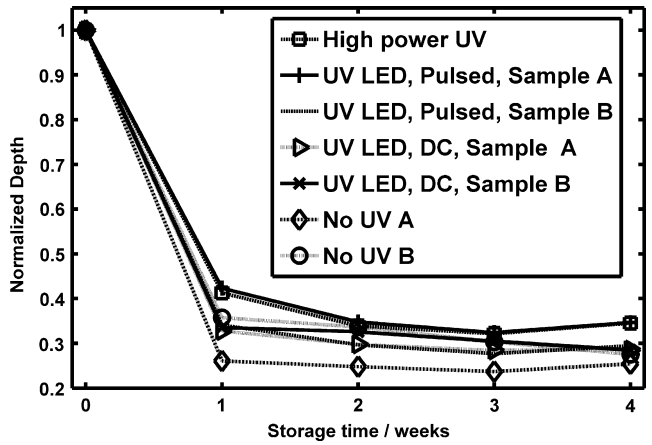

Fig. 8. Normalized scratch depth of HPMC films stored at a high relative humidity (75% RH) and at 23 ± 1 °C as a function of aging time. The values are average of single sample (three scratches). A commercial UV pistol was used to irradiate the high power samples (see text for specifications).

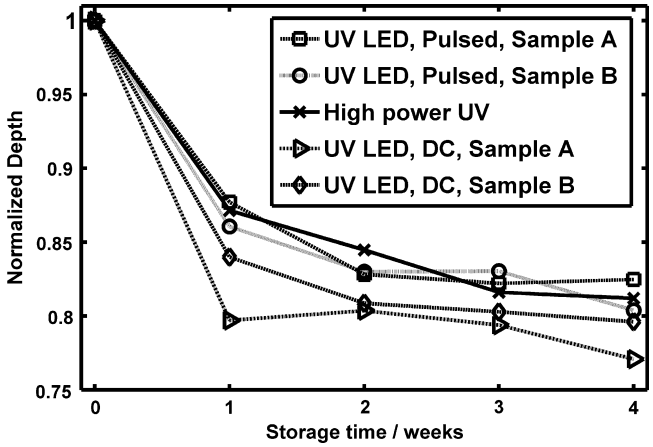

Fig. 9. Normalized scratch depth of HPMC films stored at a high temperature (50 °C) as a function of aging time. The values are average of single sample (three scratches). A commercial UV pistol was used to irradiate the high power samples (see text for specifications).

time. The measured average depths are shown in Fig. 7, whereas Figs. 8 and 9 depict single measurements (indicated with labels A and B). The standard deviations for the absolute scratch depths are 1–15%, whereas the standard deviations of the normalized depth values are smaller (1–5%). Large deviations in dimensions between individual scratches have been reported [20]. These deviations are due to the sliding and sticking action of the tip during the scratching process, as well as to environmental factors, such as changes in humidity [20]. The uncertainty in the SWLI measurement (20 nm) is small compared to the scratch-to-scratch variation. For instance before environmental conditioning, the average scratch depth and width were 7.7 ± 1.2 μm and 275 ± 20 μm, respectively.

The scratch relaxation was smallest (19 ± 1%) for the UV-treated films stored in an oven (50 °C, sample A), probably due to polymer hardening (water evaporation from the film hardens the polymer) [1]. The UV-irradiated samples stored in a high humidity (75% RH) at room temperature (23 °C, sample B) relaxed more the samples stored at high temperature between the conditioning and the first post-storage measurement. The non-irradiated films stored at high humidity manifested the highest degree of relaxation. On average, the film relaxation for UV-conditioned films stored in high humidity ranged from 68 ± 4% (pulsed UV treatment) to 71 ± 1% (continuous UV treatment), while the value was 73 ± 2% for humidity-conditioned films without UV irradiation. Regardless of the conditioning or storage environment, the most significant amount of relaxation took place during the first week in storage. The most likely cause for the difference between samples stored in high humidity compared to those stored at high temperature is the water content in the films. Water works as a plasticizer, softening the material [1]. The present results suggest that knowing the film scratch depth allows estimating the effect of environmental conditions to the scratch hardness during aging. This knowledge could be used to predict how the coating resists scratch damage during storage.

Polymers change from exhibiting glass-like properties to showing rubber-like characteristics at the glass transition temperature T_g [24]. The T_g value depends on the plasticizer type and content, including water [25]. The relaxation behavior seen in the samples stored at high temperature might be due to changes in glass transition temperature due to water evaporation [25]. Without knowing the exact water content in the films, it is difficult to estimate the evaporation effect on T_g. A more detailed study should take into account the change in humidity during all process steps.

The effect of plasticizer amount, type, and environmental aging on scratch hardness is discernible by SWLI-enhanced scratch testing. However, since the method is partly destructive (scratching) and time consuming (approximately 10 s to 1 min per measurement), it cannot as such currently be applied for online measurement as a process analytical technology (PAT). Method development is required to achieve PAT ability.

4. Conclusions

The scratch resistance of aqueous HPMC films is greatly dependent on both the amount and type of plasticizer used in the film composition. The scratch depth can be used to predict the effect of environmental conditions on relaxation during aging. With aged aqueous HPMC films plasticized with glycerol, the most significant relaxation takes place during the first week after scratching. Interferometric 3D imaging quantitatively characterizes scratch relaxation in plasticized film samples. The next step is to apply the scratch characterization measurement to film-coated tablets.

Table 1
Average scratch depth in micrometers (μm) and the number of measured scratches.

Conditioning/t	After scratching	1 week	2 weeks	3 weeks	4 weeks	Number of measured scratches (N)
No UV, 75%	6.43 ± 0.70	2.00 ± 0.50	1.89 ± 0.50	1.77 ± 0.40	1.72 ± 0.30	12
LED, pulsed, 75%	8.37 ± 1.00	3.24 ± 0.87	2.73 ± 0.70	2.54 ± 0.60	2.71 ± 0.60	6
LED, pulsed, 50 °C	8.13 ± 1.23	7.05 ± 1.00	6.74 ± 1.00	6.72 ± 1.00	6.61 ± 0.95	6
LED, DC, 75%	7.72 ± 0.70	2.56 ± 0.30	2.41 ± 0.36	2.28 ± 0.34	2.21 ± 0.30	6
LED, DC, 50 °C	7.65 ± 0.45	6.28 ± 0.65	6.17 ± 0.40	6.11 ± 0.40	6.00 ± 0.50	6
High power, 75%	8.00 ± 0.23	3.30 ± 0.15	2.71 ± 0.13	2.57 ± 0.10	2.76 ± 0.12	3
High power, 50 °C	9.66 ± 0.15	8.42 ± 0.05	8.16 ± 0.22	7.89 ± 0.2	7.85 ± 0.15	3

References

[1] M.E. Aulton, M.H. Abdul-Razzak, The mechanical properties of hydroxypropyl methylcellulose films derived from aqueous systems. Part 1: the influence of plasticizers, Drug Dev. Ind. Pharm. 7 (1981) 649–668.

[2] J. Heinämäki, V.-M. Lehtola, P. Nikupaavo, J.K. Yliruusi, The mechanical and moisture permeability properties of aqueous-based hydroxypropyl methylcellulose coating systems plasticized with polyethylene glycol, Int. J. Pharm. 112 (1994) 191–196.

[3] T. Nagai, S. Obara, H. Kokubo, N. Hoshi, Application of HPMC and HPMCAS to aqueous film coating of pharmaceutical dosage forms, in: J.W. McGinity (Ed.), Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, Marcel Dekker Inc., New York, 1997, pp. 177–225.

[4] J.W. McGinity, Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, Informa Healthcare, Berlin, 1996.

[5] X. Gu, T. Nguyen, L.-P. Sung, M.R. VanLandingham, M.J. Fasolka, J.W. Martin, Advanced techniques for nanocharacterization of polymeric coating surfaces, J. Coat. Technol. Res. 1 (2004) 191–200.

[6] C. Gauthier, R. Schirrer, Time and temperature dependence of the scratch properties of poly(methylmethacrylate) surfaces, J. Mater. Sci. 35 (2000) 21–2130.

[7] C. Gauthier, S. Lafaye, R. Schirrer, Elastic recovery of a scratch in a polymer surface: experiments and analysis, Tribol. Int. 34 (2001) 469–479.

[8] C. Gauthier, A.L. Durier, C. Fond, R. Schirrer, Scratching of a coated polymer and mechanical analysis of a scratch resistance solution, Tribol. Int. 39 (2006) 88–98.

[9] T.C. Ovaert, B.R. Kim, J. Wang, Multi-parameter models of the viscoelastic/plastic mechanical properties of coatings via combined nanoindentation and non-linear finite element modeling, Prog. Org. Coat. 47 (2003) 312–323.

[10] T. Bussemer, N.A. Peppas, R. Bodmeier, Time-dependent mechanical properties of polymeric coatings used in rupturable pulsatile release dosage forms, Drug Dev. Ind. Pharm. 29 (2003) 623–630.

[11] L.-P. Sung, P.L. Drzal, Metrology for characterization scratch resistance of polymer coatings, J. Coat. Technol. Res. 2 (2005) 583–589.

[12] C. Xiang, H.-J. Sue, J. Chu, B. Coleman, Scratch behavior and material property relationship in polymers, J. Polym. Sci. Polym. Phys. 39 (2001) 47–59.

[13] A. Hult, A. Krupicka, M. Johansson, G. Favaro, Mechanical surface characterization: a promising procedure to screen organic coatings, J. Coat. Technol. Res. 75 (2003) 19–27.

[14] I. Kassamakov, K. Ojala, A. Salmi, E. Hæggström, J. Aaltonen, A. Huber, H. Saarikko, M. Österberg, M. Oinonen, Proc. SPIE (2006). 61881G-1.

[15] T. Dresel, G. Häusler, H. Venzke, Three-dimensional sensing of rough surfaces by coherence radar, Appl. Opt. 31 (1992) 919–925.

[16] G.S. Kino, S.S.C. Chim, Mirau correlation microscope, Appl. Opt. 29 (1990) 3775–3783.

[17] G.T. Lim, M.-H. Wong, J.N. Reddy, H.-J. Sue, An integrated approach towards the study of scratch damage of polymer, J. Coat. Technol. Res. 2 (2005) 361–368.

[18] J.C. Russ, The Image Processing Handbook, CRC Press, Boca Raton, 1995. pp. 214–216.

[19] P. Rangarajan, M. Sinha, V. Watkins, K. Harding, Scratch visibility of polymers measured using optical imaging, Polym. Eng. Sci. 43 (2003) 749–758.

[20] M. Wong, G.T. Lim, A. Moyse, J.N. Reddy, H.-J. Sue, A new test methodology for evaluating scratch resistance of polymers, Wear 256 (2004) 1214–1227.

[21] M. Wong, A. Moyse, F. Lee, H.-J. Sue, Study of surface damage of polypropylene under progressive loading, J. Mater. Sci. 39 (2004) 3293–3308.

[22] J. Rajesh, J. Bijwe, Investigations on scratch behaviour of various polyamides, Wear 259 (2005) 661–668.

[23] B.J. Briscoe, P.D. Evans, S.K. Biswas, S.K. Sinha, The hardnesses of poly(methylmethacrylate), Tribol. Int. 29 (1996) 93–104.

[24] I.M. Ward, D.W. Hadley, An Introduction to the Mechanical Properties of Solid Polymers, John Wiley and Sons Ltd., Chichester, 1993. p. 174.

[25] B.C. Hancock, G. Zografi, The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids, Pharm. Res. Dord. 11 (1994) 471–477.