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Research paper

Novel analytical methods for the characterization of oral wafers

Verena Garsuch, Jörg Breitkreutz *

Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Düsseldorf, Germany

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ABSTRACT

This study aims at compensating the lack of adequate methods for the characterization of the novel dosage forms buccal wafers by applying recent advanced analytical techniques. Fast-dissolving oral wafers need special methods for assessing their properties in drug development and quality control. For morphologic investigations, scanning electron microscopy (SEM) and near-infrared chemical imaging (NIR-CI) were used. Differences in the distribution of the active pharmaceutical ingredient within wafers can be depicted by NIR-CI. Film thickness was determined by micrometer screw and coating thickness gauge revealing no significant differences between the obtained values. To distinguish between the mechanical properties of different polymers, tensile test was performed. Suitable methods to predict disintegration behaviour are thermomechanical analysis and contact angle measurement. The determination of drug release was carried out by three different methods. Fibre-optic sensor systems allow an online measurement of the drug release profiles and the thorough analysis even within the first seconds of disintegration and drug dissolution.

1. Introduction

Most recently, the buccal route is getting more and more awareness for the application of active pharmaceutical ingredients (API). The application via the buccal route offers different advantages [1–4]: an easy application, no degradation of API by gastrointestinal fluids, bypassing the first-hepatic metabolism and potentially improved bioavailability in order to ensure rapid invasion and fast onset. Many advantages of this route have been recently recognized and various dosage forms are under development [5–8]. There are not only drug-loaded films (buccal wafers), but also other dosage forms like orally disintegrating tablets (ODTs) and oral lyophilisates. Many different API have been tested [1]. The permeation of drugs could be facilitated by using penetration enhancers [9]. In the literature, the preparation of buccal films is described by different manufacturing processes: solvent casting [10], extrusion [11] or spraying processes [12]. The process of the film formation by solvent casting method has been thoroughly described [13]. Different categories of wafers are existent: flash release, mucoadhesive melt away and mucoadhesive sustained-release oral patches. By using more than one layer, even unidirectional drug transport can be achieved. The film thickness after drying should not exceed 70 μm to avoid an unpleasant feeling in the mouth [10]. A few methods for the analysis of oral wafers have been already proposed [14], including mucoadhesion measurements [15]. However, the measurement of mucoadhesion for fast-dissolving oral wafers is not very useful because the film rapidly dissolves during the measurement. A classical method for characterization is the determination of the swelling index [16,17]. Film thicknesses are measured by micrometer screw [18] or by using light microscopy [19]. Commonly, dissolution testing is performed with an unphysiological dissolution volume of a few hundred milliliters [17,20]. Furthermore, modified dissolution setup with dissolution media of less than 100 mL are still under development [21,22]. Mechanical properties of buccal wafers have been tested using a texture analyzer [18]. Furthermore, a disintegration measurement setup for fast-dissolving oral dosage forms, in this case ODTs, has been described using texture analyzer as well [23], but this setup cannot be transferred to buccal wafers.

In this study, the focus was on extending the existent methods and developing new methods for the characterization of fast-dissolving buccal wafers. The chosen model drug caffeine is buccally well absorbed [24] and has a practical designation in the treatment of apnea and bradycardia in premature infants [25]. Due to this fact, hazardous organic solvents were avoided in the development and manufacturing. The developed buccal wafers were characterized by various newly developed analytical and physiochemical techniques which are divided in terms of morphological, mechanical, disintegration and dissolution properties.

2. Materials and methods

2.1. Materials

The following substances were used as received. Caffeine anhydrous (Caesar & Loretz, Hilden, Germany) was used as API. Several

* Corresponding author. Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Universitätsstrasse 1, 40225, Düsseldorf, Germany. Tel.: +49 21181 10678; fax: +49 21181 14251.
E-mail address: joerg.breitkreutz@uni-duesseldorf.de (J. Breitkreutz).

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substances were used as film-forming agents: pullulan, which is a maltotriose (ABCR GmbH & Co. KG, Karlsruhe, Germany). A polyethylene glycol–polyvinyl alcohol copolymer (Kollicoat® IR, BASF AG, Ludwigshafen, Germany), gelatin (GELITA®, Typ B, 260 Bloom, Ph.Eur., GELITA Europe, Eberbach, Germany) and a polyvinyl alcohol (Mowiol® 4-88, Carl Roth GmbH + Co. KG, Karlsruhe, Germany) were used as film formers, as well. Furthermore, different types of Hypromellose (hydroxypropyl methyl cellulose, HPMC) Metolose® 65SH-1500 (Synthapharm GmbH, Mülheim/Ruhr, Germany), PHARMACOAT® 615 (Shin Etsu Chemical Co., Ltd., Tokyo, Japan) and Walocel® HM 6 PA 2910 (viscosity of a 2% aqueous solution: 6 mPa s) as well as HM 50 PA 2910 (50 mPa s) from DowWolff Cellulosics (Bomlitz, Germany) were used. Sucralose (InnTense™ SL 6210, InnoSweet, Braunschweig, Germany) was used as a sweetener. Glycerol 85% (Caesar & Loretz, Hilden, Germany) and sorbitol (Sorbidex® P5, Cerestar, Krefeld, Germany) were used as plasticizers to allow casting of the film solution. Polysorbat 80 (Tween® 80) and Brij® 35 (both Uniqema, Bromborough, UK) were used as surfactants. Citric acid (Dr. Paul Lohmann GmbH KG, Emmerthal, Germany) served as a saliva stimulant. All ingredients of disintegration and dissolution media were of analytical grade.

2.2. Methods

2.2.1. Preparation of buccal wafers

According to the patent literature and preliminary experiments, different basic formulations were developed, a verum formulation (A) and a placebo formulation (B). Varying amounts of film formers (depending on their gel forming properties) were incorporated into the same basic formulation (see Table 1). The film casting solution was prepared by dissolving the excipients in the solvent. The solution was heated up to 60 °C. The polymer was added and dissolved. It was cooled to room temperature by continuously stirring. In case of the drug-loaded films, caffeine was added during stirring and completely dissolved.

Accordingly, the film solutions were cast on an Erichsen film applicator (Coatmaster 509/1, Erichsen, Hemer, Germany) with a speed of 6 mm/s. Different widths from 550 to 900 μm were utilized to obtain a drug load of 10 mg per wafer for the verum formulation. The cast films were dried in an oven at 40 °C between 2 and 8 h until dryness. Individual wafers were prepared by cutting the films into pieces of regular dimension of 2 × 3 cm with a surgical scalpel and stored under controlled conditions (25 °C, 60% relative humidity).

2.2.2. Morphological studies

2.2.2.1. Scanning electron microscopy (SEM). Upper and lower side of the obtained films were gold sputtered for 180 s (Agar Manual Sputter Coater B7340, Agar Scientific Ltd., Stansted, Essex, UK). Afterwards, the distribution of caffeine and differences between upper and lower side of the films was examined by scanning electron microscopy (Leo 1430 VP, Leo Elektron Microscopy, Cambridge, UK) at a working voltage of 20 kV.

2.2.2.2. Near-infrared chemical imaging (NIR-CI). The samples and powder substances were analyzed with the SyNIRgi® (Malvern, Worcestershire, United Kingdom), a near-infrared chemical imaging digital analyzer, which builds on the Spectral Dimensions Sapphire®/NIRCI-2450 platform. 81920 NIR spectra can be generated from a 13 mm × 10 mm sample area in 2 min. The spectral range was 1200–2450 nm and the detector size was 320 × 256 pixels. The drug-loaded films were imaged with the 40 μm/pixel object lens. The images were taken at a band of 1670 nm. Statistical and image analysis were conducted by ISys®, the Malvern's data analysis software. Differences between the drug-loaded films referring to the distribution of active substance and possible recrystallizations were visualized.

2.2.3. Mechanical properties

2.2.3.1. Film thickness. Film thicknesses were determined using two different methods. The measurement with the micrometer screw (Mitutoyo, Neuss, Germany) is product contacting in comparison with the coating thickness gauge (Minitest 600, Erichsen, Hemer, Germany), which is a contact-free method. Each wafer was measured at five positions (central and the four corners) and the mean thickness was calculated.

2.2.3.2. Tensile strength. The force at tearing and elongation was measured during tensile test by a universal testing apparatus (H10KM, Hess, Sonsbeck, Germany) using a load cell of 1000 N. Each strip of the films was cut and prepared according to the standard DIN EN ISO 527 [26]. The test specimen No. 2 was clamped between the tensioning tools. The drawing rate was 50 mm/min and no preload was used. Tensile strain at break (%) and tensile stress at break (MPa) were calculated [27].

2.2.4. Disintegration

2.2.4.1. Thermomechanical analysis – swelling. Swelling was measured by thermomechanical analysis (TMA) using a Mettler TA 3000 Apparatus (Mettler Toledo, Gießen, Germany) with TC 10A Processor and a TMA 40 load cell. Discs were film coated with either placebo or verum film solutions, each with the same width (900 μm). A film-coated disc was placed into a crucible and was annealed. The measuring sensor was placed onto the surface with a constant force of 0.02 N at a constant temperature of 37 °C. Using a syringe 250 μL of purified water was added.

2.2.4.2. Contact angle measurement. Drop shape analysis was used to determine contact angles. Time-dependent contact angles were measured by an optical contact angle meter (Drop Shape Analysis

Table 1
Composition of the investigated film solutions. (A) Shows the composition of drug-loaded films and (B) displays the formulations for placebo wafers, content in (%).

	Polymer	Caffeine anhydrous	Sucralose	Sorbitol	Glycerol 85%	Citric acid	Tween® 80	Brij® 35	Alcohol 96%	Water	Total
Panel A											
Gelatin	13.24	3.65	0.51		3.57	0.45				78.58	100
Walocel® HM 6 PA 2910	13.24	3.65	0.51		3.57	0.45			39.29	39.29	100
Walocel® HM 50 PA 2910	7.08	3.90	0.55		3.83	0.48			42.08	42.08	100
Metolose® 65SH-400	2.46	4.10	0.57		4.02	0.51			44.17	44.17	100
Mowiol® 4-88	13.24	3.65	0.51		3.57	0.45			39.29	39.29	100
Pullulan	13.17	3.63	0.51		3.55	0.45	0.49			78.20	100
Panel B											
Metolose® 65SH-1500	4.59			2.28	0.91	0.46	0.08	0.30	45.69	45.69	100
Walocel® HM 6 PA 2910	10.67			2.14	0.86	0.43	0.07	0.29	42.77	42.77	100
Walocel® HM 50 PA 2910	4.91			2.28	0.91	0.46	0.08	0.30	45.53	45.53	100
Pharmacoat® 615	6.00			2.25	0.90	0.45	0.08	0.30	45.01	45.01	100
Kollicoat® IR	19.31			1.93	0.77	0.39	0.06	0.26	38.64	38.64	100

System DSA100, Krüss, Hamburg, Germany) at room temperature. Distilled water of volume 7.5 μL was dropped onto the film lying planar on the surface. The contact angle was determined after 30 s by using the supplied software (Drop Shape Analysis DSA1 v 1.90, Hamburg, Germany).

2.2.5. Drug release

The in vitro drug release of the wafers was determined using the USP 24 apparatus type 2 (Sotax AT6, Sotax GmbH, Lörrach, Germany). The dissolution medium was 250 mL of phosphate buffer pH 6.0 according to the Ph. Eur. 6.2 dissolution test for medicated chewing gums. The rotation speed was 50 rpm at 37 °C. The drug release was analyzed spectrophotometrically at 272 nm. One film was placed into each vessel. The measurement was replicated five times with the standard deviation as a measure of variation.

2.2.5.1. Fibre-optic sensor system. A fibre-optic submersible sensor (T300-RT-UV–VIS, Mikropack, Ostfildern, Germany) was dipped into the medium. The obtained absorptions during drug release were measured online via spectrometer (USB4000-UV–VIS, Mikropack, Ostfildern, Germany). Spectra between 200 and 800 nm were recorded and analyzed.

2.2.5.2. Common dissolution apparatus with manual sample withdrawing. Every 30 s, 0.5 mL samples were manually withdrawn and measured by UV–VIS spectroscopy (Spekol 1200, Analytik Jena, Jena, Germany). The withdrawn amount of dissolution medium was calculated.

2.2.5.3. Common dissolution apparatus with modified withdrawing of samples. Samples were withdrawn automatically by a peristaltic pump, analyzed by a spectrometer at 272 nm (Lambda 2S, Perkin–Elmer, Juegesheim, Germany) and returned. The lag time was determined to be 15 s.

3. Results and discussion

3.1. Morphological studies

3.1.1. Scanning electron microscopy

SEM images were taken to visualize the surface morphology of the wafers. In these pictures, differences can be seen between upper (a + c) and lower (b + d) surface, as well as differences between the polymers (Fig. 1). Caffeine tends to recrystallize, which was found for both polymer films. In the case of pullulan wafers (a), caffeine recrystallizes as large needles. Mowiol® 4-88 films (c) show smaller needle sizes. As can be expected, the recrystallization tendency is more likely on the upper side (a + c) than on the lower side (b + d) of the film. This fact enforces the difference in roughness between upper and lower sides and has to be considered for further investigations like surface pH or mucoadhesion measurements.

3.1.2. Near-infrared chemical imaging

NIR-CI is a non-invasive approach to analyze the distribution of substances within the wafers. Therefore, the films had to be calibrated against the pure substances. In this case, the respective polymer and the active ingredient caffeine were analyzed separately. For both substances suitable vibrational bands for selective imaging could be detected. During the manufacturing of the wafers recrystallization processes took place and NIR-CI was used to clarify whether the polymer, the active ingredient or one of the excipients recrystallized. Due to the small amount of excipients, they could be excluded. In Fig. 2 two different images of polymeric wafers can be seen. While polymer and active ingredients are distributed very inhomogenously within the pullulan wafer (a), the film made of HPMC (b) is very homogenous. There are lots of small agglomerates of caffeine (marked by arrows), in which caffeine is surrounded by a dark area which is the polymer. During the drying process, the caffeine recrystallizes and the area around the crystals impoverishes. It should be considered that each API might need an appropriate polymer formulation.

The NIR-CI is also quite interesting for active ingredients which do not recrystallize.

3.2. Mechanical properties

3.2.1. Film thickness

For these investigations only caffeine-free formulations were used. The usage of two independent measuring methods was chosen to investigate their accuracy. The thicknesses of wet films (data not shown) decrease about 86–97% compared to the dried films. The thickness of the films made of Walocel® HM 50 PA 2910, measured by the coating thickness gauge, mostly diminishes with

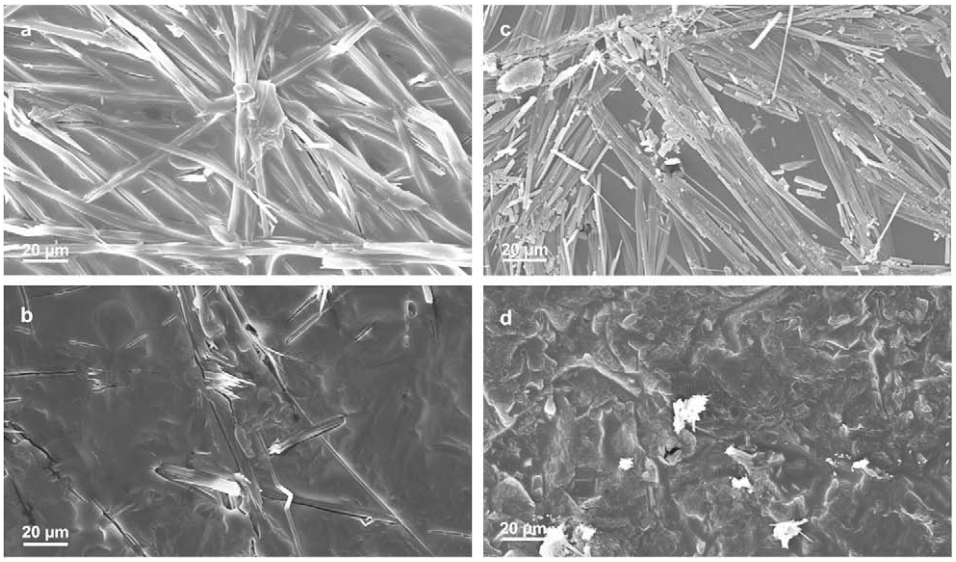

Fig. 1. Scanning electron micrographs of polymer films containing caffeine, upper (a) and lower (b) side of a pullulan film, upper (c) and lower (d) side of a polyvinyl alcohol film (Mowiol® 4-88).

97.1%. The Kollicoat® IR films showed the lowest solvent loss, the thickness decreased about 85.7%, measured with the micrometer screw. Intermediate values were found for buccal films made of the remaining polymers. All the polymers, with the exception of pullulan, showed no differences between the methods used (Fig. 3). Wafers made from pullulan showed an average dry film thickness of 32.92 μm measured by the coating thickness gauge, while the determination by micrometer screw revealed a value of 48.92 μm. Statistical analysis revealed that there is no significant difference ($p > 0.05$) between these two methods. Depending on the polymer, it should be considered that different measuring methods lead to differences between the obtained values. In most cases, careful measurement with the micrometer screw offers the same accuracy as the measurement with the coating thickness gauge.

3.2.2. Tensile strength

Aim of this part of the study was to distinguish between the used polymers, without changing ratio of the excipients, especially the polymers, and to identify variations in the mechanical characteristics. A quality control test should be developed as it is commonly used in the plastics industry. Therefore, DIN EN ISO 527 was applied using No. 2 test specimen. Tensile test was performed to assess strength and elasticity of the prepared films. In dependence of the cut film strip, different results arise. Well-established parameters are tensile strength (σ_M) as well as modulus of elasticity in tension (E_t). In our study, the tensile strain at break (ε_B) and the tensile stress at break (σ_B) were analyzed, at which the tensile stress at break (σ_B) is identical to the tensile strength (σ_M). Buccal wafers are desirable with a high tensile strength and a low modulus of elasticity [18]. According to the use of a test specimen all film strips broke in the middle and not at the clamps. Table 2 displays the mechanical properties of caffeine-content film preparations. Wafers made of gelatin showed highest values in ε_B and σ_B, which means that these films are hard and tough. Film strips made of Metolose® 65SH-400 are soft and weak. Due to the fact that the films made of Metolose® 65SH-400 showed the smallest film thickness (data not shown), it is not surprising that they broke at the lowest force of about 2.40 MPa. The high standard deviations arise from the fact that the active ingredient recrystallizes. Recrystallization occurs overall the dried film, and large crystals grow at the expense of the smaller ones.

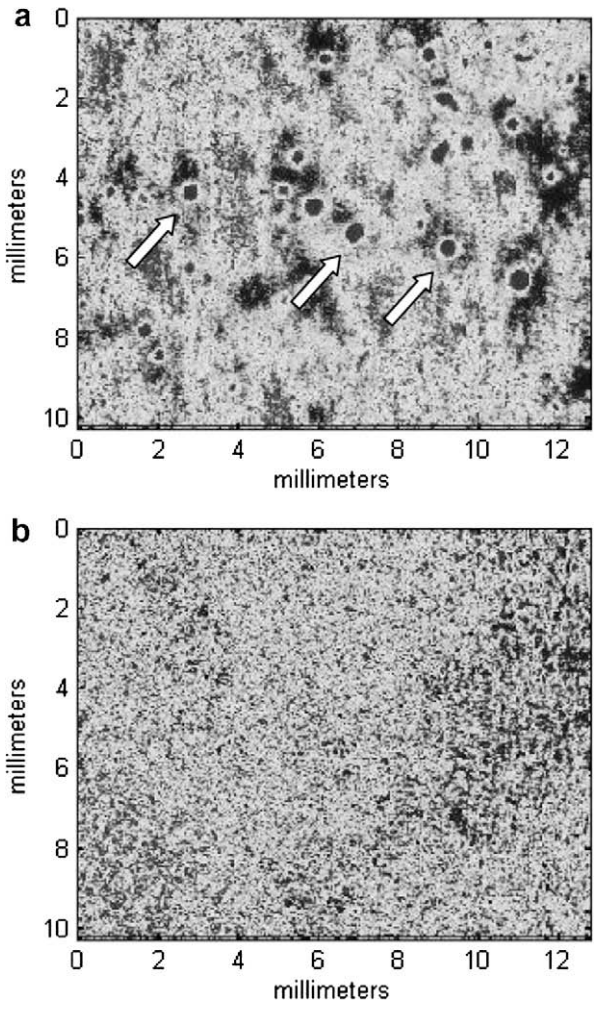

Fig. 2. NIR chemical images of drug-loaded oral films. (a) Pullulan film with recrystallized caffeine and (b) HPMC film with homogenously distributed caffeine.

3.3. Disintegration measurements

3.3.1. Thermomechanical analysis – swelling

Swelling is defined as expansion in aqueous media. In the case of buccal wafers, the films swell and dissolve subsequently, so it is no swelling process in the common sense. The developed setup was applied to predict the disintegration behaviour. In our study, the swelling process is finished when the sensor dips onto the surface of the metallic disc. The results for the polymer HPMC at two different degrees of polymerization are shown (Fig. 4). In (a) and (b), both API-free formulations show initial swelling and dissolve afterwards. While the addition of caffeine hardly influences the curves of HM6PA2910, HM50PA2910 with API shows a completely different behaviour. The film-coated discs with the drug-loaded formulation did not swell, but rather dissolved instantly. Although the discs of the two polymers were filmed with the same width of 900 μm wet film thickness, there were differences between the dried discs. HM6PA2910 films (a) had dry thicknesses between 65 μm (drug-free discs) and 85 μm (drug-loaded discs), while discs of HM50PA2910 (b) lie between 28 μm (drug-free) and 65 μm (drug-loaded). Furthermore, the negative values after complete dissolution result from the fact that the discs did not have exact the same thicknesses, so the zero balance did not fit exactly with every disc. Other polymers like gelatin also behave like HM6PA2910 with hardly any differences between API-free and drug-loaded discs. Results of Mowiol® 4-88 offered similar graphs of API-free and drug-loaded curves, but in completely different *y*-axis intercept.

3.3.2. Contact angle measurement

The drop shape analysis apparatus records a movie for the measurement of contact angles. The movie starts automatically if the drop passes a predetermined mark. Afterwards images at different time points, here at time point 0 and after 30 s (Fig. 5), were evaluated. The contact angle can be measured by different methods like the two tangential methods, a height–width ratio, the circle fitting and the sessile drop fitting. In this study, the height/width ratio was used. With this method, the height and width of the drop shape is determined. If the contour line is enclosed by a rectangle and seen as a segment of a circle, the contact angle can be calculated from the ratio of height to width of the rectangle. The determination was impossible if the wetting agent (phosphate buffer) penetrated into the film completely. As can be seen in Fig. 6, within all investigated polymers the contact angle changes during measurement due to the drops sinking into the surface of the films. Gelatin films are hardly wetted by phosphate buffer within 30 s, the contact angle decreases from 66.0° to 60.3°. The same behaviour showed by HM50PA2910 with a decrease from 37.0° to 32.8°. On the other hand, the contact angles of Mowiol® 4-88

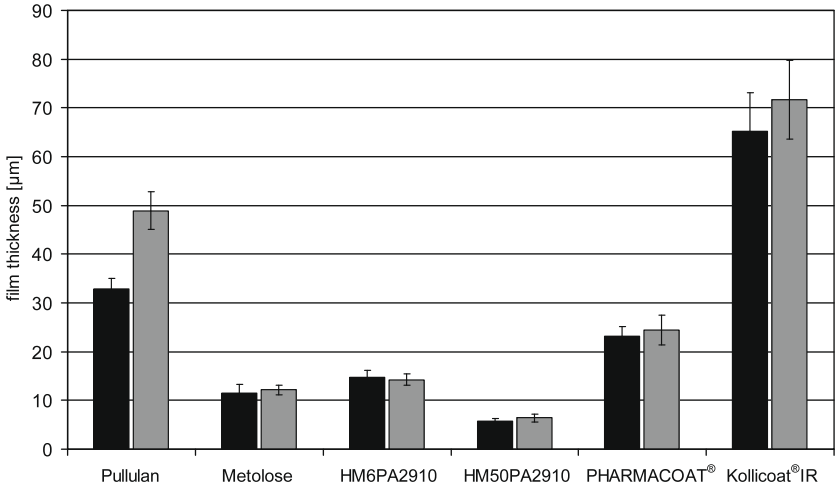

Fig. 3. Film thicknesses of drug-free films, left: coating thickness gauge, right: micrometer screw, mean ± SD, $n = 5$.

Table 2
Tensile testing with tensile strain at break (%) and tensile stress at break (MPa) (mean ± SD, $n = 5$).

	ε_B Tensile strain at break (%)	σ_B Tensile stress at break (MPa)
Gelatin	11.77 ± 3.722	20.22 ± 6.395
Walocel® HM6PA2910	6.46 ± 1.946	12.32 ± 3.709
Walocel® HM50PA2910	4.43 ± 2.607	11.08 ± 6.519
Metolose® 65SH-400	0.49 ± 0.205	2.40 ± 1.015
Mowiol® 4-88	3.09 ± 0.572	5.15 ± 0.953
Pullulan	3.74 ± 1.286	7.74 ± 2.661

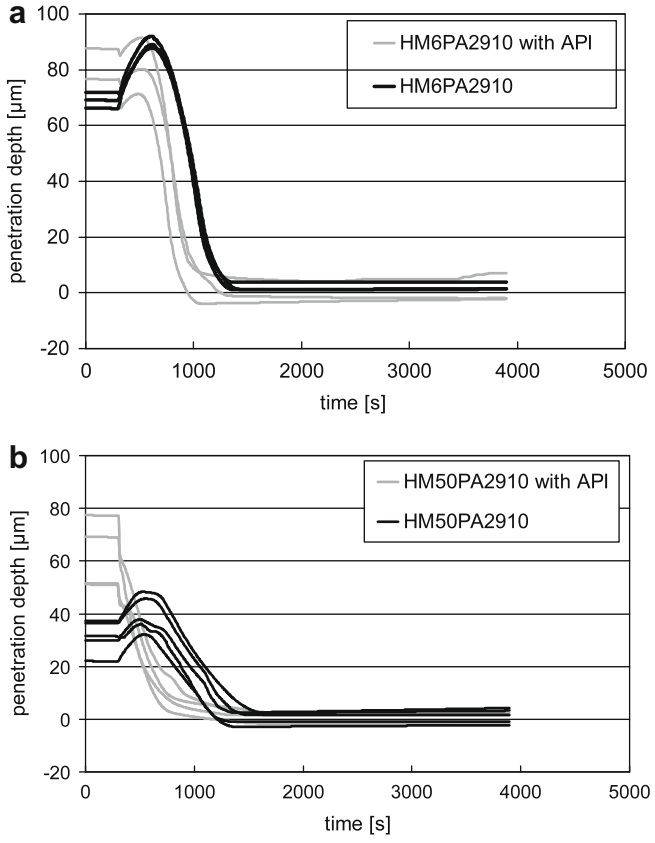

Fig. 4. Swelling behaviour of HPMC (a) HM6PA2910 and (b) HM50PA2910. Swelling fluid was 250 µL purified water (37 °C).

(29.2°) and pullulan (34.1°) decreased that much within 30 s that a determination could not be conducted. A centered position with a decrease from 23.1° to 6.9° showed by HM6PA2910. The received results could allow possible predictions for the wetting behaviour and, hence, the drug disintegration and dissolution of oral wafers.

3.4. Drug release

In all the tested methods, the wafers dissolved completely within 250 s (Fig. 7). Depending on the polymer type and the film width, the dissolution profiles differ. The measurements with the fibre-optic sensor and the common dissolution apparatus with manual sample withdrawing did not consider the deviations from actual to nominal API content. The different positions of the wafer within the vessel are a problematical issue. After setting the wafer into the vessel, the film is located at different places: at the paddle, at the vessel, at the surface, at the sample withdrawer or sensor or – preferably – at the bottom side.

3.4.1. Fibre-optic sensor system

The fibre-optic sensor system allows an online measurement without sample withdrawing. Due to the volume of 250 mL of phosphate buffer pH 6.0, the positioning of the sensor is difficult. On the one hand, a correct sample withdrawing according to the European Pharmacopoeia should be ensured and, on the other hand, the sensor should not be touched by the paddle. So another reason for the high standard deviations could be the position of the sensor. The release rate of 87.1% from pullulan films and 92.5% of gelatin films (a) is caused by the deviation from actual to nominal content. The content was determined by HPLC, but as shown before caffeine tends to recrystallize and, therefore, the high deviations could arise. While pullulan films show the lowest release rate, the gelatin films show the slowest drug release profile (a). The other three polymers in descending order achieve the following release rates: Mowiol® 4-88 (107.3%), with the fastest and highest drug release, HM50PA2910 (105.6%) and HM6PA2910 with 101.9% of the nominal content (a).

3.4.2. Common dissolution apparatus with manual sample withdrawing

The common dissolution apparatus with a manual sample withdrawing only allows a sample withdrawing in 30 s intervals, because it is not feasible to obtain samples within shorter time intervals. The samples are withdrawn by a bulb pipette and diluted prior to the measurement with a spectrometer. The missing disso-

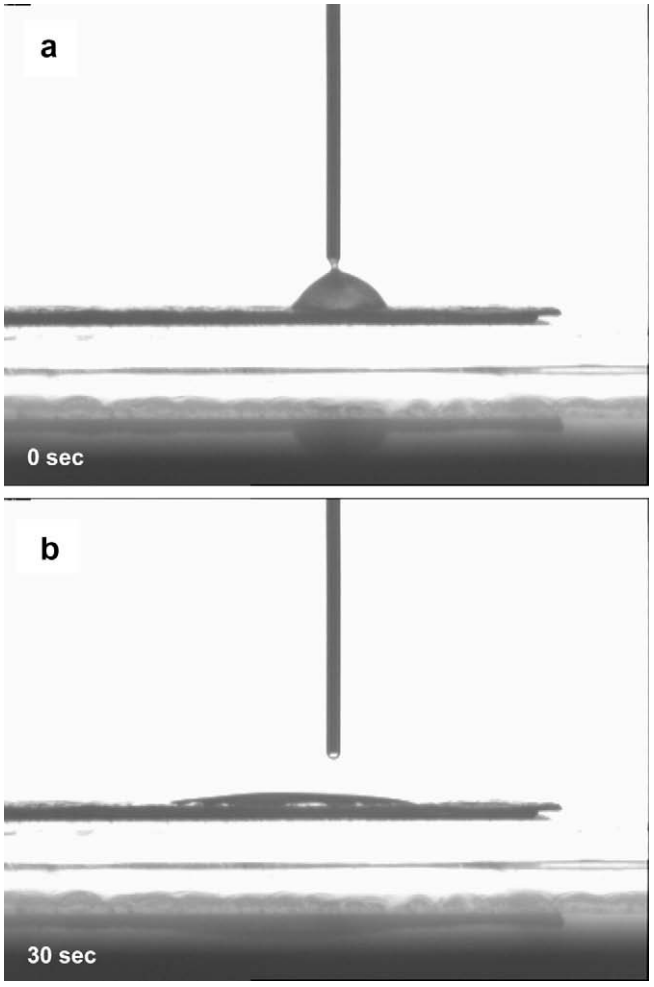

Fig. 5. (a) and (b) show images of drug-loaded Mowiol® 4-88 films during contact angle measurement at different time points.

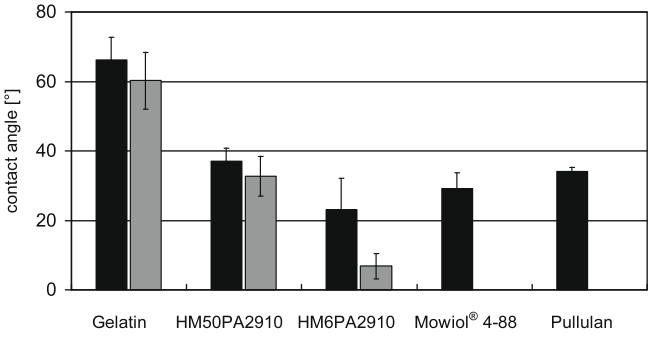

Fig. 6. Contact angles measured of verum formulations with phosphate buffer pH 6.0 as wetting fluid, left: measurement after 0 s, right: measurement after 30 s, mean ± SD, $n = 5$.

lution volume has to be considered and calculated within the values. The standard deviations are similar to that of the fibre-optic sensor. The release rates are inferior compared to the sensor method due to variations between actual and nominal content of the wafers. Within 250 s gelatin films released 84.5%, Mowiol® 4-88 wafers 90.9%, pullulan wafers 91.6%, HM6PA2910 99%, and HM50PA2910 101.7% (b), although all the wafers were completely dissolved. The slowest and lowest drug release was shown by gelatin films, while HM6PA2910 showed fastest and highest drug release at time point 180 s (b). A main disadvantage of the presented method is the lesser number of sample withdrawing of maximal nine times within the 250 s.

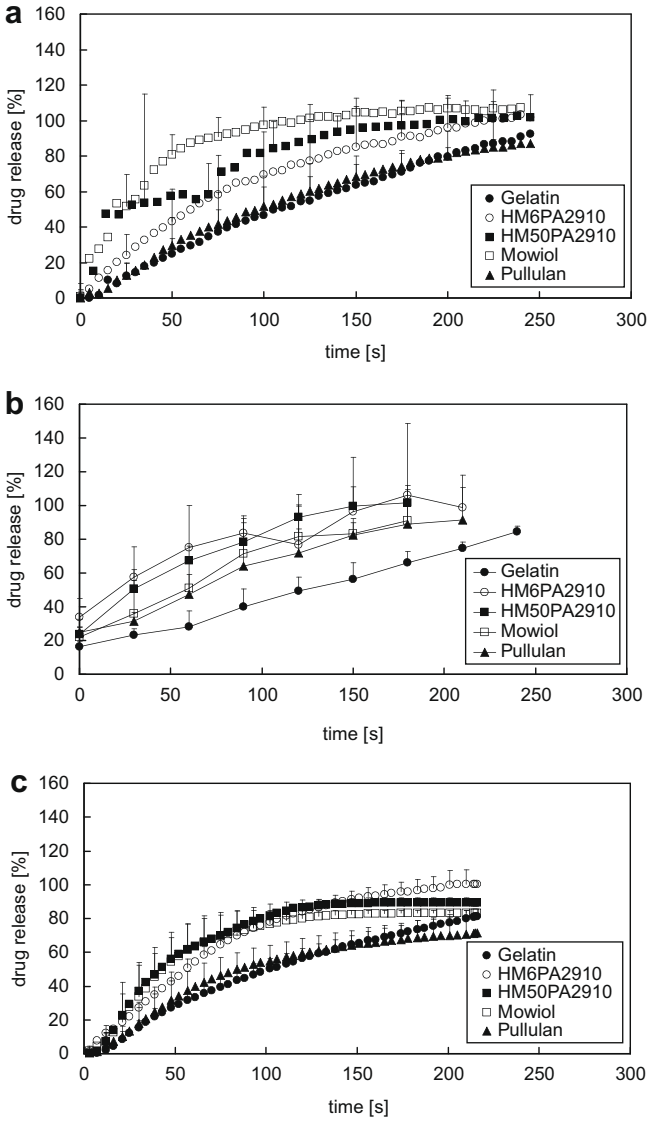

Fig. 7. Comparison of three dissolution setups. Fibre-optic sensor system (a), common dissolution apparatus with manual drawing of samples (b) and dissolution apparatus with modified drawing of samples (c) at 37 °C, 50 rpm, medium: 250 mL phosphate buffer pH 6.0, mean + SD, $n = 5$.

3.4.3. Common dissolution apparatus with modified withdrawing of samples

Due to the missing of sample withdrawing no difficulties in the performance existed when using the fibre-optic sensor system. In contrast, the common dissolution apparatus with modified withdrawing of samples exhibited several problems. The wafers often stuck at the filters and gave incorrect results. These curves show rapidly increasing values and decreased afterwards and, therefore, were not included into the analysis. Furthermore, it must be considered that it is not an online measurement, which is actually important for a fast-dissolving dosage form. The dissolution medium has to pass tubes and in order to do that the lag time varies. In this study, short tubes were used so the lag time was only 15 s. Although in this measurement setup the actual content was considered, the release rates are still too low (c). The lowest value showed pullulan with 71.3% release rate, followed by gelatin films

(81.2%) with the slowest drug release and Mowiol® 4-88 with 83.1%. The 100% value was only achieved by HM6PA2910 (100.4%) which shows against highest drug release. HM50PA2910 showed 89.4% drug release rate after 250 s.

A method which closely observes the drug release was only achieved with the fibre-optic sensor system and the common dissolution apparatus with modified withdrawing of samples. Samples are withdrawn every second and a precise diagram of the dissolution behaviour can be presented. The curves of both methods are similar. Calculations of the obtained data revealed that the drug release from buccal wafers follow a square root kinetics. The common methods with manual withdrawing of samples and modified withdrawing of samples by continuous pumping by a peristaltic pump are less suitable for fast-dissolving dosage forms than compared to the fibre-optic sensor system.

4. Conclusions

Buccal wafers are interesting novel dosage forms and their use will definitely expand in the future. There is a demand of one or more monographs in the pharmacopoeias. Therefore, new analytical methods and quality control tests are necessary. In the presented study, new and advanced methods for the characterization of buccal wafers are shown. Doubtless, there are still some lacks in the performance. Among other things, it is quite important to standardize an artificial saliva as a uniform release medium, analogous to the gastric juice, and thus to enable comparative studies at different labs. It was shown in the present paper that modern methods for visualization of the API distribution within the films (SEM, NIR-CI) or the disintegration behaviour (TMA, contact angle measurement) may identify product or batch variations where conventional techniques fail. There are still some improvements required regarding the determination of drug release kinetics.

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References

[1] L.I. Giannola, V. De Caro, G. Giandalia, M.G. Siragusa, G. Campisi, Current status in buccal drug delivery, Pharm. Tech. Eur. (May) (2008) 32–39.
[2] J.D. Smart, Buccal drug delivery, Expert Opin. Drug Deliv. 2 (2005) 507–517.
[3] J. Swarbrick, Buccal absorption of drugs, in: J. Swarbrick, J.C. Boylan (Eds.), Encyclopedia of Pharmaceutical Technology – Absorption of Drugs to Bioavailability of Drugs and Bioequivalence, Marcel Dekker, New York, 1988, pp. 189–208.
[4] M.E. de Vries, H.E. Boddé, J.C. Verhoef, H.E. Junginger, Developments in buccal drug delivery, Crit. Rev. Ther. Drug Carrier Syst. 8 (1991) 271–303.
[5] M. Ciper, R. Bodmeier, Modified conventional hard gelatin capsules as fast disintegrating dosage form in the oral cavity, Eur. J. Pharm. Biopharm. 62 (2006) 178–184.
[6] O.A. Scholz, A. Wolff, A. Schumacher, L.I. Giannola, G. Campisi, T. Ciach, T. Velten, Drug delivery from the oral cavity: focus on a novel mechatronic device, Drug Discov. Today 13 (2007) 247–253.
[7] L. Perioli, C. Pagano, S. Mazzitelli, C. Rossi, C. Nastruzzi, Rheological and functional characterization of new antiinflammatory delivery systems designed for buccal administration, Int. J. Pharm. 356 (2008) 19–28.
[8] G.C. Ceschel, V. Bergamante, I. Orienti, G. Zuccari, C. Ronchi, A. Fini, Mucoadhesive gels for buccal administration of chlorhexidine digluconate, in: Proc. 5th World Meeting in Pharm., Biopharm. and Pharm. Techn., Geneva, 2006.
[9] J.A. Nicolazzo, B.L. Reed, B.C. Finnin, Buccal penetration enhancers – how do they really work?, J Control. Release 105 (2005) 1–15.
[10] H.G. Zerbe, A.J. Serino, J.-H. Guo, Sofortige Benetzbarkeit aufweisende(r) wasserlöslicher Film oder wasserlösliche Schicht zur oralen Applikation, European Patent EP1362584, 2003.
[11] V.S. Tumuluri, M.S. Kemper, I.R. Lewis, S. Prodduturi, S. Majumdar, B.A. Avery, M.A. Repka, Off-line and on-line measurements of drug-loaded hot-melt extruded films using Raman spectroscopy, Int. J. Pharm. 357 (2008) 77–84.
[12] R.S. Davidson, G.S. Kehoe, Water-soluble film for oral use, European Patent EP1532973, 2005.
[13] F.K. Alanazi, A.A. Abdel Rahman, G.M. Mahrous, I.A. Alsarra, Formulation and physicochemical characterisation of buccoadhesive films containing ketorolac, J. Drug Deliv. Sci. Technol. 17 (2007) 183–192.
[14] F. Cilurzo, I.E. Cupone, P. Minghetti, F. Selmin, L. Montanari, Fast dissolving films made of maltodextrins, Eur. J. Pharm. Biopharm. 70 (2008) 895–900.
[15] I.W. Kellaway, In vitro test methods for the measurement of mucoadhesion, in: R. Gurny (Ed.), Bioadhesion, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1990, pp. 86–92.
[16] K.G.H. Desai, T.M. Pramod Kumar, Preparation and evaluation of a novel buccal adhesive system, AAPS PharmSciTech 5 (2004).
[17] H. Okabe, E. Suzuki, Y. Sugiura, K. Yanagimoto, Y. Takanashi, M. Hoshi, E. Nogami, K. Nakahara, T. Sekiguchi, M. Baba, E. Saitoh, Development of an easily swallowed film formulation, Int. J. Pharm. 355 (2008) 62–66.
[18] K.K. Peh, C.F. Wong, Polymeric films as vehicle for buccal delivery: swelling, mechanical, and bioadhesive properties, J. Pharm. Sci. 2 (1999) 53–61.
[19] C. Juliano, C.L. Pala, M. Cossu, Preparation and evaluation of polymeric films containing propolis, J. Drug Deliv. Sci. Technol. 17 (2007) 177–181.
[20] N.A. Nafee, F.A. Ismail, N.A. Boraie, L.M. Mortada, Mucoadhesive buccal patches of miconazole nitrate: in vitro/in vivo performance and effect of ageing, Int. J. Pharm. 264 (2003) 1–14.
[21] A. Dinge, M. Nagarsenker, Formulation and evaluation of fast dissolving films for delivery of triclosan to the oral cavity, AAPS PharmSciTech 9 (2008) 349–355.
[22] S. Charde, M. Mudgal, L. Kumar, R. Saha, Development and evaluation of buccoadhesive controlled release tablets of lercanidipine, AAPS PharmSciTech 9 (2008) 182–190.
[23] R. Bohnacker, F. Streil, S. Schweizer, I. Müller, Bestimmung der Zerfallszeit von Schmelztabletten mit Hilfe der Texture-Analyser-Methode, Pharm. Ind. 67 (2005) 327–335.
[24] G.H. Kamimori, C.S. Karyekar, R. Otterstetter, D.S. Cox, T.J. Balkin, G.L. Belenky, N.D. Eddington, The rate of absorption and relative bioavailability of caffeine administered in chewing gum versus capsules to normal healthy volunteers, Int. J. Pharm. 234 (2002) 159–167.
[25] T. Stephenson, Caffeine for neonates, Paed. Perinat. Drug Ther. 1 (1997) 46–49.
[26] Deutsches Institut für Normung, DIN EN ISO 527 Teil 3 – Bestimmung der Zugeigenschaften, 2003.
[27] Deutsches Institut für Normung, DIN EN ISO 527 Teil 1 – Bestimmung der Zugeigenschaften, 1996.