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Research paper

Formulation development of a continuously manufactured orodispersible film containing warfarin sodium for individualized dosing

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ABSTRACT

Continuously manufactured orodispersible films (ODFs) offer a promising approach for individualized therapy with an easy to administer solid dosage form. The aim of this study was to develop a long ODF containing warfarin sodium to enable safe and more flexible dosing. Formulation development was conducted systematically for the continuous film coating process. A continuously working pilot-scale coating bench was used for film manufacturing and the viscosities of the polymer solutions were investigated to obtain processible formulations. The investigation of the mechanical properties of the long film was an integral part of the study, because the handling of the long film during flexible dosing differs distinctly from the handling of a single dosed ODF. The secant modulus and the yield stress were evaluated as parameters with high information value about the deformation behavior of the ODF. A long warfarin ODF was successfully produced using the pilot-scale coating bench equipped with an optical probe for in-line film thickness measurement. It was feasible to use the principle of a tape dispenser for flexible and, therefore, individualized dosing as proof of concept. Combining the long ODF with a dosing device allows individualized therapy with warfarin for all age groups manageable by the patient himself.

1. Introduction

Individualized medicine as flexible treatment of patients is of great relevance and interest. This is because of inter- and intraindividual differences due to variations in age, body functions and ethnic diversity as well as pharmacogenetics and pharmacogenomics. A well-known active pharmaceutical ingredient (API) that is subject to dose individualization is the anticoagulant warfarin sodium (hereafter referred to as “warfarin”). It is widely used for the prevention and treatment of thromboembolic diseases in adults as well as children beginning at age 0 [1]. On top of its narrow therapeutic index, the coumarin derivative shows highly inter- and intraindividual variation in the drug response [2]. Variations in the genes of enzymes affecting the warfarin drug action lead to varying degrees of warfarin resistance or varying capacity for metabolizing the API resulting in higher risk of side effects like bleeding complications or difficulties in starting the warfarin therapy [3,4]. It has been shown that there are different warfarin requirements in diverse ethnical groups [5] as well as in children [6]. Having this in mind, a special need for individualized therapy of warfarin is obvious and it is used as model drug in this study. Currently, individualized therapy with warfarin is only possible by injection or splitting tablets. Only the British National Formulary for children describes a “Specials” formulation for a liquid dosage form, namely an oral suspension with 1 mg/ml warfarin sodium [7]. This further illustrates the current need of a formulation that can be dosed flexibly. Especially for children there is an urgent need for an age appropriate formulation as the Paediatric Committee of the European Medicines Agency states in their “Inventory of paediatric therapeutic needs” [8].

To realize the general implementation of individualized medicine, easily applicable dosage forms are required that allow flexible dosing. Especially solid dosage forms for oral drug delivery, as the most important and accepted route of administration are of great interest [9]. Solid dosage forms such as tablets or capsules show advantages over liquid dosage forms, such as higher stability and better dosing accuracy. Dosing flexibility, however, is worse and drug intake is more uncomfortable for some patients for the solid dosage form due to swallowing difficulties.

A solid dosage form that combines the dosing flexibility of liquid dosage forms with less difficulties in swallowing are orodispersible films (ODFs). They are defined in the European Pharmacopoeia as

Abbreviations: API, active pharmaceutical ingredient; AV, acceptance value; HPC, hydroxypropyl cellulose; HPLC, high performance liquid chromatography; HPMC, hydroxypropyl methylcellulose; ODF, orodispersible film; PVA, polyvinyl alcohol

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"single- or multilayer sheets of suitable materials, to be placed in the mouth where they disperse rapidly" [10]. Lacking large pieces after dispersion, they can be swallowed without swallowing difficulties and fear of choking [11]. The administration of ODFs requires practically no consumption of water, which is beneficial for people on the road and for patients dealing with volume restrictions due to illness [12]. The dose adaption of ODFs is easily attained by cutting the film into different sized pieces containing the desired amount of API [13]. The most common manufacturing process of ODFs is the solvent casting technique. The film forming solution, containing one or more polymers as well as the API and optional ingredients like plasticizers, fillers or taste masking agents, is cast onto an intermediate liner, dried and then cut in the desired size and shape [14]. There are small-scale film coating benches available that can be used non-continuously for small batches as well as machines that work continuously [11,15,16].

Wening and Breitkreutz developed a general classification for solid and liquid dosage forms and their dosing devices for individualized therapy. Individual doses can be realized either by accumulation of small drug carriers (e.g. counting pellets or mini-tablets, liquid droppers) or by partition of a bigger drug carrier (e.g. tablet splitting, solid dosage pen, syrup) [17]. The combination of a long oral film with a dosing device would fill a gap pointed out by Wening and Breitkreutz as an alternative dosage form that would be less critical than splitting tablets. The aim of this work was, therefore the development of a long ODF containing warfarin that could be implemented in individualized therapy. The continuously working pilot-scale film manufacturing process employed in this study enables the small-scale production of long films. This long ODF can be cut in a filmstrip with defined width that in turn can be cut into pieces with varying length leading to flexible dosing. To perform flexible dosing at the point of care, a device is crucial for the step of cutting the long film into the desired length. ODFs would be a better formulation of warfarin for pediatric and geriatric patients because of its easy intake and impossibility to spit it out. An important goal of combining a long ODF with a dosing device is that the flexible dosing can be performed by the patient himself or a caregiver directly at the point of care. The flexible dose adaption allows a quick and easy reaction on changing dose requirements. No medical staff and no additional production step is necessary to obtain individualized doses with this idea, compared to using printing techniques for personalization of warfarin therapy [18]. This work was conducted as a systematic approach of the long oral film formulation development by evaluating different formulations regarding their suitability for the processing on the continuously working pilot-scale coating bench. Furthermore, the ODF needed to possess certain properties like specific mechanical behavior to be suitable for dose adaption in a tape dispenser as cutting device for proof of concept.

2. Materials and methods

2.1. Materials

Hypromellose (hydroxypropyl methylcellulose, HPMC, Pharmacoat 606, Shin-Etsu, Tokyo, Japan), hydroxypropyl cellulose (HPC, Klucel EXF, Ashland, Covington, USA) and polyvinyl alcohol (PVA, PVA 26-88, Merck, Darmstadt, Germany) served as film forming polymers. As plasticizers glycerol 85% (Caesar&Loretz, Hilden, Germany), citric acid (Panreac, Castellar del Vallès, Spain) and triethyl citrate (Jungbunzlauer, Basel, Switzerland) were used. Freshly distilled water was used as solvent for the polymer solutions. The incorporated active ingredient was warfarin sodium (Farmak, Olomouc, Czech Republic).

2.2. Polymer solutions

2.2.1. Preparation of the polymer solutions

A batch size of 500 g was prepared for manufacturing of eight meter long orodispersible films. For the HPMC and the HPC solutions, the plasticizer was dissolved in cold water, the polymer was added and stirred until the polymer was fully dissolved. Solutions containing PVA were heated up to 90 °C after adding the polymer to the cold water to fully dissolve the polymer. In case of a combination of PVA and HPMC, HPMC was dispersed in the warm PVA solution and the combination cooled down while stirring. Plasticizer was added to the cold polymer solution. The solution containing warfarin was heated to 80 °C before adding the polymer (HPMC) to reduce the preparation time. Plasticizer and warfarin were added after cooling and complete dissolution of the polymer. Evaporated water was added in the end to the cold solutions.

2.2.2. Viscosity of the polymer solutions

Rheological measurements of the polymer solutions were performed with a rheometer (Kinexus pro+, Malvern, Worcestershire, UK) using a cone (1°, 60 mm) and plate setting (65 mm). A shear ramp was recorded from 0.1 to 100 s^{-1} and 100 to 0.1 s^{-1}. The temperature was set to 25 °C and each sample was measured three times. To compare the samples, the viscosity at a shear rate of 4 s^{-1} was chosen. This value represents the settings of the coating process (gap height and liner speed) representing the shear rate applied during the film coating [16].

2.3. Continuous manufacturing of orodispersible films

Continuous film manufacturing was performed with a pilot-scale coating bench (MBCD TGM-K-1.4, Optimags, Dr. Zimmermann, Karlsruhe, Germany, Fig. 1). The polymer solution was pumped through the coating knife and cast on the non-siliconized side of the intermediate liner (Silphan S75M, Siliconature, Godega di Sant'Urbano, Italy) using a gap height of 500 µm for the placebo films. To obtain acceptable content uniformity, the real wet film thickness of the warfarin film was controlled by an in-line film thickness measurement (see Section 2.4) and precisely adjusted to 250 µm. The liner with the applied coating mass moved through the 80 cm long drying tunnel with a speed of 12.5 cm/min. The drying tunnel consisted of two heating zones of equal size that could be independently adjusted. Drying temperature was set to 90 °C for the first heating zone and to 110 °C for the second heating zone. The drying time for the film resulted in 6.4 min for these basic process settings. The liner with the dried ODF was coiled up at the end [16].

2.4. In-line film thickness

A sensor equipped with an optical probe (CHRocodile S, Precitec, Gaggenau-Bad Rotenfels, Germany) with a measuring range of 3 mm and a chromatic confocal measuring principle was used for in-line measurement of the film thickness [16]. At the continuous coating bench, the probe was positioned directly after the coating knife to measure the thickness of the wet coating mass (Fig. 2).

2.5. Cutting of ODF samples

For precise cutting of the ODF samples for further characterizations a cutting plotter (Cameo® 3, Silhouette America, Lindon, USA) was used [16]. The samples of the placebo films were cut from the whole width of the film except of two centimeters of the peripheral regions, which minimized differences in the film thickness due to surface effects of the polymer solutions. The samples from the warfarin film were further cut over the whole length of the produced film to evaluate the homogeneity of the API content and other properties of the film throughout the process. Using the Silhouette Studio® software (version 4.0.837ss, Silhouette America, Lindon, USA) the shape of the sample (2 * 2.5 cm and 2 * 12 cm rectangles) was created and send to the plotter. The AutoBlade (Silhouette America, Lindon, USA) was used, which automatically adjusted the chosen blade settings entered in the software. Cutting thickness and cutting speed were selected matching the properties of the ODF. The lowest thickness level (1 out of 10) and a low

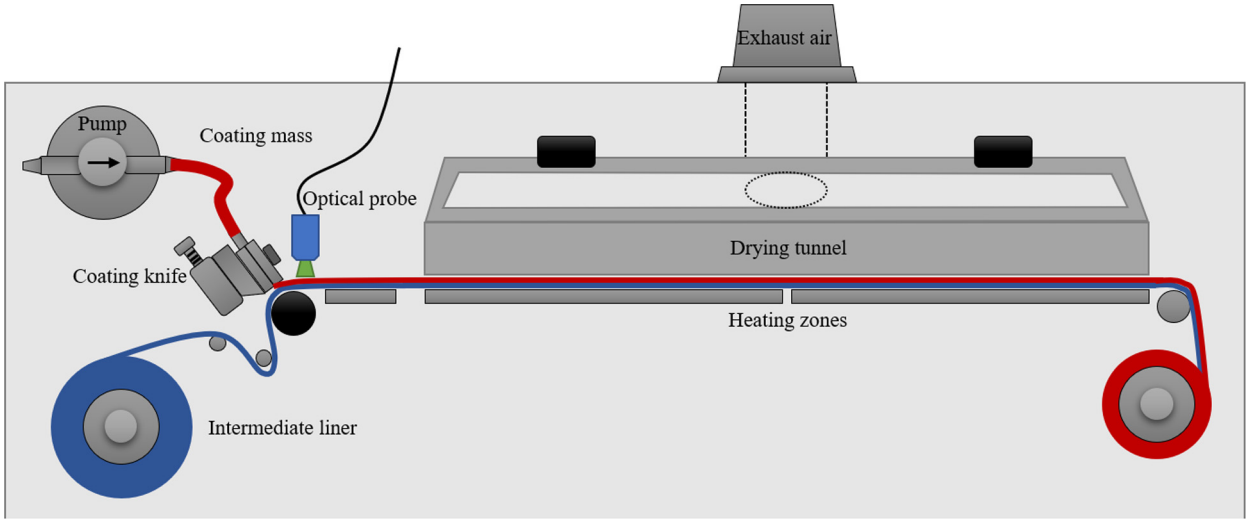

Fig. 1. Schematic view of the continuously working pilot-scale coating bench for long oral film manufacturing equipped with an optical probe for wet film thickness measurements [16]. Used by courtesy of the International Journal of Pharmaceutics, Elsevier.

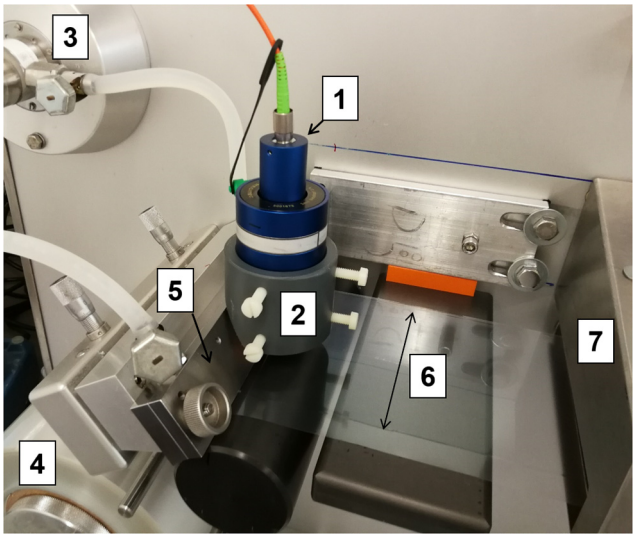

Fig. 2. Picture from Niese and Quodbach [16]: Assembly of the optical probe at the pilot-scale coating bench. Showing the probe head (1), probe head mount (2), pump (3), intermediate liner (4), coating knife (5), coated film on the liner (6) and the drying oven (7). Used by courtesy of the International Journal of Pharmaceutics, Elsevier.

speed (3 out of 10) were sufficient to obtain good results for cutting the film without cutting the intermediate liner.

2.6. Characterization of the ODFs

2.6.1. Storage of samples

Film samples were stored in closed plastic bags at 21 °C after production.

2.6.2. Mechanical properties

The mechanical properties of the films were investigated by performing a tensile test according to standard DIN EN ISO 527-1 and -3 [19,20]. A texture analyser (TA.XTplus, Stable Micro Systems, Godalming, UK) was used to characterize a rectangular test specimen (2 * 12 cm). The specimen was fixed between the upper and lower clamp with a distance of 10 cm. The test speed was set to 0.1 mm/s. The test lasted until the sample broke. The measurement was repeated five times for each batch. The force-distance diagram was recorded,

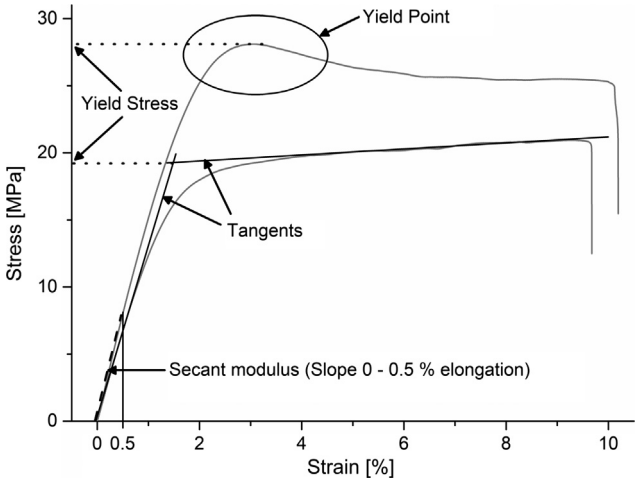

Fig. 3. Exemplary diagram of two different stress-strain curves. With and without yield point. Dotted line: yield stress determination. Dashed line: secant modulus determination.

transformed into a stress-strain diagram and the secant modulus, according to ASTM D882 [21] as the slope of the linear range between 0 and 0.5% strain, and the yield stress as the stress at the transition from elastic to plastic deformation were determined (Fig. 3). The yield stress was obtained from the stress-strain diagram in two different ways depending on the shape of the curve. If the curve showed a yield point the maximum stress at this point was used. If the curve did not show a yield point, the yield stress was visually identified, applying two tangents to the linear arms of the curve and determining the stress at the intercept of the tangents (Fig. 3).

2.6.3. Disintegration time

Disintegration time of the ODFs was determined using the “slide frame” method [22]. A film (2 * 3 cm) was inserted into a slide frame, which was then placed horizontally on a beaker. 200 µl of distilled water of 37 °C were placed on the film using a pipette. The time until the drop disintegrated the film and fell into the beaker was recorded. For each batch six samples were measured.

2.6.4. Dynamic vapor sorption

Water absorbency of the different film samples was investigated using a dynamic vapor sorption system (SPS 11, ProUmid, Ulm,

Germany). The samples were dried at 0% relative humidity and subsequently the relative humidity was increased in steps of 10% until it reached 90% relative humidity. Each step lasted until the weight of every sample was at equilibrium (weight change < 0.01%/30 min). Measurements were performed once for every batch.

2.6.5. Water content by Karl Fischer titration

Residual water content of the films was determined via Karl Fischer titration using a Volumetric KF Titrator (Mettler-Toledo, Gießen, Germany). As working medium, Hydranal-Methanol dry (Honeywell, Offenbach, Germany) was used. The titration was performed with Hydranal-Composite 5 (Honeywell, Offenabch, Germany). Hydranal-Water Standard 10.0 (Honeywell, Offenbach, Germany) was used for calibration purposes. Measurements were performed three times for every batch.

2.6.6. Warfarin sodium assay

The warfarin sodium content was determined using high performance liquid chromatography (HPLC). The method was modified from the United States Pharmacopoeia official monograph (USP 39) and validated according to the ICH guideline Q2 [23]. An Elite LaChrome System (Hitachi-VWR, Darmstadt, Germany) was used that consisted of a pump L-2130, an autosampler L-2200, an oven L-2300 and an UV-Detector L-2400. It was equipped with a 125 mm long Nucleosil® 120-3 RP-18 column (Machery-Nagel, Düren, Germany) that was operated at 40 °C oven temperature. A mixture of methanol/water/glacial acetic acid (64:36:1) served as mobile phase and the flow rate was set to 0.7 ml/min. The warfarin content of the ODF was determined by dissolving one film (2 * 2.5 cm) in 25.0 ml of distilled water, filtering the sample through a 0.45 µm pore sized polypropylene membrane filter and injecting 15 µl. The API was detected at a wavelength of 280 nm. For each batch ten films were measured for the evaluation of the content uniformity.

2.6.7. Stability testing of warfarin sodium ODF

Stability testing of the warfarin sodium ODF was performed after storing samples at two climatic conditions. Unpacked samples for warfarin sodium assay (2 * 2.5 cm, 2.5 mg label claim, n = 10) and for testing of mechanical properties (2 * 12 cm, n = 5) were stored at 21 °C and 40% relative humidity and at 21 °C and 60% relative humidity for twelve weeks. Examinations of the assay and the mechanical properties were performed every four weeks according to Sections 2.6.2 and 2.6.6.

2.6.8. Statistical evaluation

Statistical data evaluation was performed using Microsoft Excel 2013 (Mircrosoft Corporation, Redmond, US) containing the data analysis add in (Analysis ToolPak, Mircrosoft Corporation, Redmond, US). *F*-tests and *t*-tests were performed for a significance level of $\alpha = 0.05$. Depending on the result of the *F*-test, the p-value was determined by either using the *t*-test for assuming equal variances or for assuming unequal variances.

3. Results and discussion

3.1. Development approach

Following a systematic approach for the development of the long ODF with warfarin, the authors screened the literature for different polymers and plasticizers to be investigated. As common film formers for fast dissolving oral films HPMC, HPC and PVA were chosen for this study as discussed in several reviews and publications [14,24–27]. Glycerol, triethyl citrate and citric acid served as plasticizing agents and were investigated in different concentrations. Viscosity studies were performed for the polymer solutions and mechanical tests were performed for the finished ODFs and the results used as quality attributes. The first investigations for an ODF containing warfarin were performed with placebo formulations due to the high toxicity of the API. The preparation was meant to be composed as simple as possible to enable the use in pediatric patients as a possible target group for individualized therapy with warfarin. The investigated formulations are displayed in Table 1.

Table 1
Film formulations for placebo film investigations. Percentages refer to the complete formulation (w/w).

Formulation	Film former [%]		Plasticizer [%]		Cast film
H1	HPMC	17.5	–		x
H2			Glycerol	3	x
H3			Glycerol	2	x
H4			Triethyl citrate	3	x
H5			Triethyl citrate	2	x
H6			Citric acid	3	x
H7			Citric acid	2	x
P1	PVA	10	–		–
P2			Glycerol	5	–
P3		12.5	–		–
P4			Glycerol	5	–
P5			Glycerol	2	–
PH1	PVA: HPMC	12.5 (1:1)	–		–
PH2			Glycerol	2	–
PH3		12.5 (2:1)	–		–
PH4			Glycerol	2	–
PH5		15 (2:3)	–		x
PH6			Glycerol	1	x
PH7			Triethyl citrate	1	x
PH8			Citric acid	2	x
HPC	HPC	20	–		x

3.2. Placebo formulation development

3.2.1. Viscosity of polymer solutions

Thabet and Breitkreutz report a threshold value of 1 Pa*s for the viscosity of polymer solutions when producing an orodispersible film on the continuously working pilot-scale coating bench used in this study [15]. At lower viscosities the solution flows down at the wrong side of the coating knife without forming a film on the intermediate liner. Therefore, the first step in the formulation development was to adjust the viscosity to reach the aforementioned threshold (Fig. 4). No adjustment was required for HPMC formulations (17.5% polymer content) since they were based on published data [15]. Concentration variations were necessary for pure PVA formulations that did not show a sufficient viscosity with a polymer content of 10% (P1). Although glycerol increased the viscosity, the threshold was not fulfilled for P2 as well. Therefore, the polymer content was raised to 12.5%. The following PVA formulations showed satisfying viscosities (P3-P5). The combination of PVA and HPMC with a polymer content of 12.5% and a ratio of 1:1 resulted in a too low viscosity that did not improve by adding plasticizer (PH1 and PH2). A change in the polymer ratio and a concentration increase were necessary to reach the threshold of 1 Pa*s (PH3-PH8). The HPC solution exceeded the threshold with a polymer content of 20%. All polymer solutions with a viscosity above 1 Pa*s were processible on the pilot-scale coating bench in this study, whereas formulations with a lower viscosity could not be cast without problems. The mentioned threshold could be confirmed with these results.

3.2.2. Continuous manufacturing of long placebo films

After identifying processible formulations, the dried ODFs were assessed. The films that were cast and the changes that were made to the formulations are sown in Table 1. Only films with satisfying properties were considered for further investigations. Satisfying films showed a homogenous appearance without holes and a constant coating width. They were dry at the end of production and neither did

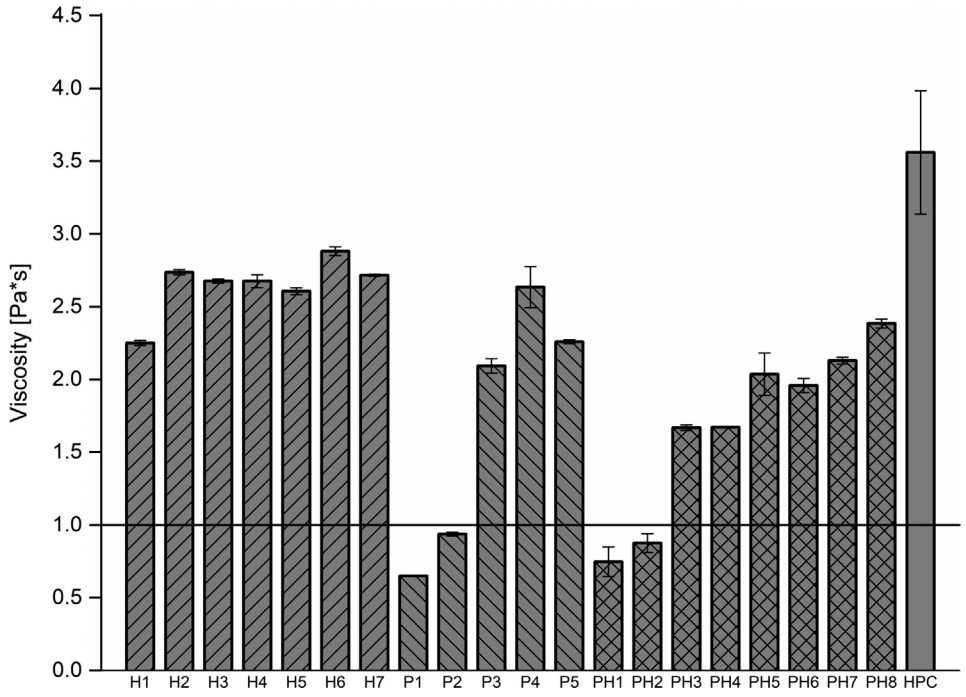

Fig. 4. Viscosities of polymer solutions measured at $4\,s^{-1}$ and 25 °C. The line represents the threshold for the viscosity [15], patterns differentiate the polymer matrices of the solutions (mean ± sd, n = 3).

they separate from the liner by themselves nor did they deform noticeably when separating them from the liner. All HPMC solutions did form satisfying films without adjustment of the basic settings. Formulation H1 separated from the intermediate liner while cutting the film with the cutting plotter, which led to uncontrolled cuts since the cutting template refers to exact coordinates on the cutting map. The formulation was therefore rejected, and improved by adding plasticizers. Plasticizer addition increased the stickiness of the film to the liner. Therefore, the following HPMC films were sufficiently sticking to the liner and cuttable by the cutting plotter. Formulation P3 did not form a satisfying coherent film but formed holes throughout the film due to surface phenomena. Potentially, a high surface tension not matching the surface free energy of the intermediate liner might be the case [28]. By adjusting the settings of the film coater it was not possible to improve this result. Adding a plasticizer did not change this aspect but additionally made the films P4 and P5 very elastic and hard to handle. These films stuck strongly to the intermediate liner and were highly deformable. Separation from the liner was only possible under deformation of the film. Because of these observations, formulations P1 to P5 were rejected. Since the viscosity of PH1 and PH2 was too low the polymer ratio was changed from 1:1 to 2:1. PH3 and PH4 formed adequate films but were too elastic for handling. They deformed extremely when separating the films from the liner and were therefore discarded and the formulation optimized further. The ratio of the film formers was changed in advantage of the HPMC to 2:3. Thus, the elastic contribution of the PVA was lowered and to achieve adequate viscosity the total polymer content was also raised to 15% (PH5-PH8). These formulations produced satisfying films. The HPC solution also showed acceptable film forming properties after increasing the pump setting due to its high viscosity.

3.2.3. Characterization of long placebo films

In the intended proof of concept dosing device the long films are coiled up, pulled and cut multiple times. This implies that the mechanical properties are very important and the requirements are different than for the commonly known single-dosed film pieces. The long ODFs must be flexible enough to be coiled up during production process as well as in the dosing device. Rupture of the film is not acceptable. Likewise, the films must be robust enough to not deform when a tensile force is applied by the patient. Neither an elastic nor a plastic deformation is acceptable since dosing is based on the film length. A deformation of the film would change the length of the original film and, therefore, the dose. To evaluate the mechanical properties of the long ODFs, two measurement values obtained from the tensile test were investigated. The secant modulus as the slope of the first part of the stress-strain diagram served as a measure for the elastic deformation behavior whereas, the yield stress served as a measure for the beginning of the plastic deformation behavior. The commonly used measurement values like tensile strength, tensile strain at break and Youngs modulus [14] were not investigated. The Youngs modulus was not included because the international standard for tensile testing of films and sheets [20] clearly points out that it is not to be used for films and sheets. Therefore, the secant modulus, which is similar to the Youngs modulus but accepted as parameter in the ASTM standard [21], was applied. The tensile strength was not investigated because the information does not represent the actual handling of the film. The tensile strength is defined as the “maximum tensile stress sustained by the test specimen during a tensile test” [19]. The maximum stress could equal the tensile stress at break as well as the tensile stress at yield, which represent two completely different points on the stress-strain curve and therefore, by just providing the single measurement value, a clear distinction could not be made. Regarding the handling of long ODFs it is a distinct difference whether the maximum stress applicable to the film causes rupture of the film or deforms it irreversibly. The tensile strain at break was rejected due to high statistical scatter arising [29] and because the first part of the stress-strain diagram is more meaningful for the mentioned purpose. Changes in the first parts of the curve are a good indicator for the deformation behavior of the film. When strong changes are observed within the first part of the curve, most likely denoting plastic deformation, this would lead to potentially harmful dosing inaccuracies already before breakage. The latter part of the curve, containing the tensile stress and strain at break is therefore not a suitable measure. Due to these reasons, the commonly used measurement values were replaced by the secant modulus and the yield stress (Fig. 3) for the

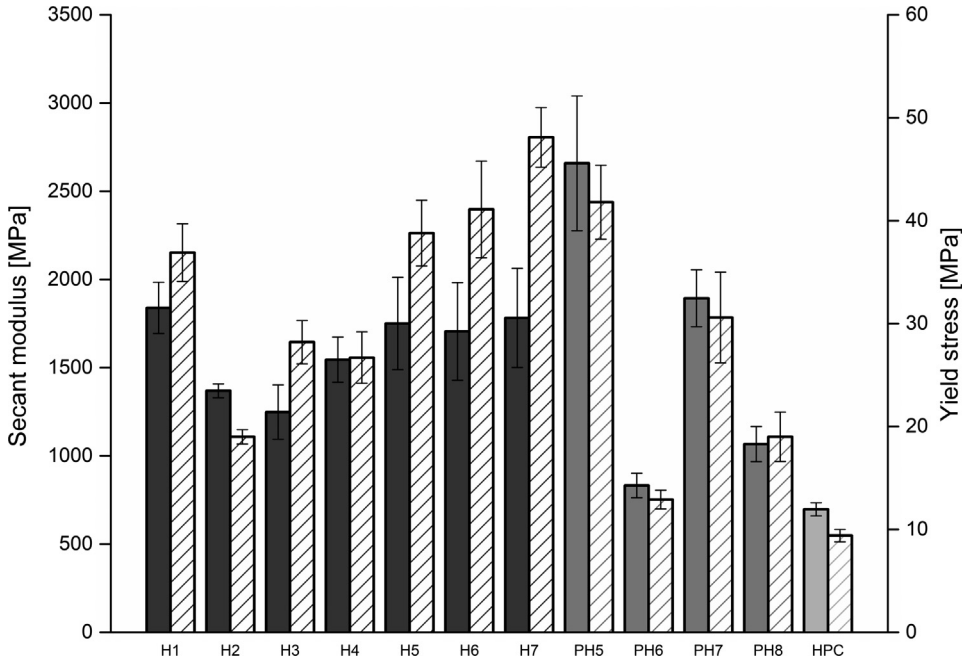

Fig. 5. Mechanical properties obtained from tensile tests of the long ODFs. Filled columns: secant modulus; dashed columns: yield stress (mean ± sd, n = 5).

Table 2
Placebo film properties. Disintegration time (mean ± sd, n = 6), water content (mean ± sd, n = 3) and water vapor sorption at 70% relative humidity (n = 1).

Formulation	Disintegration time [s]	Water content [%]	Vapor sorption [%]
H1	54 ± 12	7.43 ± 0.27	10.66
H2	32 ± 6	10.21 ± 2.34	16.86
H3	55 ± 4	4.70 ± 0.30	13.72
H4	46 ± 3	4.55 ± 0.17	7.71
H5	58 ± 2	3.54 ± 0.33	7.22
H6	54 ± 2	5.13 ± 0.19	11.27
H7	58 ± 5	4.94 ± 0.08	10.83
PH5	22 ± 5	6.77 ± 0.72	11.27
PH6	27 ± 4	8.06 ± 0.49	13.42
PH7	38 ± 3	6.08 ± 0.23	10.01
PH8	44 ± 4	3.80 ± 0.11	11.67
HPC	30 ± 4	6.11 ± 0.05	9.89

purpose of evaluating the mechanical behavior of the long ODFs. A low secant modulus points out that the region of elastic deformation is spread over a wider strain range and that the elastic deformation occurs already at low applied stresses. A low yield stress means that only little stress is needed to overcome the yield point, leading to plastic deformation. Therefore, it was important to find ODF formulations that form films with high secant moduli and yield stresses to ensure safe handling and minimum deformation and thus consistent dosing of the film. Very low measurement values that indicate high plasticity were used as exclusion criteria in this study. No threshold can be defined in this regard as it would also depend on the mechanical forces within a dosing device. Fig. 5 shows the results of the tensile test from the produced long films. To prevent the film from separating from the intermediate liner different plasticizers were added. The plasticizers led to improved sticking of the film but also changed the mechanical properties. The formulations H4, H5 and PH7, containing triethyl citrate formed satisfying films with good mechanical properties, i.e. low deformation and good flexibility without breakage. Although triethyl citrate is a plasticizer commonly used for tablet coatings also among others in pediatric formulations, due to the bitter taste the films prepared with it had to be discarded in this study. An orodispersible film rapidly dissolves in the mouth and thus a bitter taste is not acceptable, especially for children. To further work with this plasticizer taste masking investigations and formulation changes would be necessary, which were not subject of this study. Films H6, H7 and PH8, with citric acid as an alternative plasticizer showed promising results and a pleasant taste but revealed incompatibilities with the warfarin due to pH incompatibility. Two films showed inacceptable mechanical properties with a secant modulus below 1000 MPa and a yield stress below 16 MPa. HPC as well as PH6 exhibited very low secant moduli and yield stresses that indicate easy deformation of the film if a patient applied force to pull on the film. Therefore, the formulations were excluded from the study. PH5 showed high values for the secant modulus and yield stress since no plasticizer was added. This led to a very stiff film that could not be coiled up reliably. Since coiling up is essential for the use in a dosing device this film was excluded as well. The only remaining formulations were H2 and H3. For further investigations, H3 was preferred over H2 because of the higher yield stress that provided a better resistance to pulling force.

Besides the mechanical properties, further characteristics of ODFs are important for their suitability and evaluation, i.e. the disintegration time, water content and water vapor sorption (Table 2). All films showed disintegration times < 60 s and thus were beneath the threshold value of three minutes stated by the Ph.Eur. 9.3 for orodispersible tablets [30]. A threshold for the disintegration time of oral films is still lacking in the European Pharmacopoeia. Disintegration time, water content and vapor sorption were linked to each other. Films that showed higher water content and higher vapor sorption tended to have a lower disintegration time. The lower disintegration time is positive for ODFs (water vapor sorption isotherms are shown in Fig. S1 in supplementary material). The better the polymer film takes up water, the faster the disintegration can take place. But a good compromise must be found, since a too high water content and vapor sorption adversely affect the properties of the ODFs. Films with higher water content and higher vapor sorption suffer losses in their mechanical integrity due to the plasticizing effect of incorporated water. Furthermore, the films tend to get sticky, show microbiological stability issues and therefore, need to be properly packed in air tight packaging [31].

The HPMC film that was chosen because of its mechanical properties (H3) showed acceptable disintegration time within 55 ± 4 s and a water content of 4.70 ± 0.30%. The vapor sorption was rather high

due to the hygroscopic effect of the glycerol and stability at different relative humidities needed to be guaranteed by stability tests (see Section 3.3.3). On the contrary, films with citric acid as plasticizer show promising results regarding the vapor sorption. They take up less water than the films containing glycerol in similar amounts than the film without any plasticizer (Table 2, Fig. S1). For APIs not being sensitive to the acid character of the citric acid, this plasticizer is a promising alternative for the use in oral films. Additionally, it improves the taste after disintegration in the mouth, which is of great relevance for orodispersible films.

3.3. Warfarin sodium ODF formulation development

3.3.1. API incorporation

After the successful development of a placebo formulation that was suitable to cast a long film on the continuously working pilot-scale coating bench, warfarin had to be incorporated. The first trial of preparing a warfarin solution in formulation H3 led to a solution with a high viscosity of 3.24 ± 0.07 Pa*s. It was possible to process the solution on the pilot-scale coating bench but due to the higher viscosity a large amount of the film forming solution was wasted to ensure a consistent process and to obtain a smooth film. To reduce API containing toxic waste during the manufacturing process on the pilot-scale coating bench, the polymer content was lowered to 15% HPMC to reduce the viscosity. The final warfarin formulation contained 15% HPMC as film former, 2% glycerol as plasticizer, 2% warfarin and distilled water as solvent and was readily processible. The viscosity of this solution yielded 1.74 ± 0.02 Pa*s and the formulation was easy to handle in the process of continuous film coating. Table 3 shows the properties of the warfarin film. The disintegration time was improved compared to placebo film H3, which correlates with the increased water content and vapor sorption. The secant modulus did not change with the API incorporation, whereas the yield stress even slightly increased.

3.3.2. Content uniformity

A critical step in drug manufacturing in general and film manufacturing in particular is to achieve content uniformity of the dosage form. It is important that the API is evenly distributed throughout the whole film. To assure an even distribution, the polymer solutions with the dissolved API had to be thoroughly blended and the wet film thickness of the coated film had to be controlled. This was done with an optical sensor as in-line tool. The probe measured the wet film thickness of the coating mass behind the coating knife during the film casting process [16]. Using this in-line measurement tool, a precise adjustment of the wet film thickness was possible leading to a uniform long warfarin film. Using a polymer solution that contained 2% warfarin, the wet film thickness was adjusted to 250 µm to achieve a warfarin content of 0.5 mg/cm^2 in the dried film calculated with the formula stated by Krampe [32]. The drug content of the freshly produced film was determined by HPLC measurement and the acceptance value (AV) was calculated to investigate the content uniformity of the film (t0, Fig. 6). The achieved AV of 6.1 was below the threshold value of 15 indicating acceptable results for the mean content as well as the scattering of the investigated samples that were collected from the whole length of the produced film. Therefore, it was feasible to produce a homogenous long ODF containing warfarin.

Table 3
Warfarin sodium ODF properties. Disintegration time (mean ± sd, n = 6), water content (mean ± sd, n = 3) and water vapor sorption at 70% relative humidity (n = 1). Mechanical properties (mean ± sd, n = 5).

Disintegration time [s]	Water content [%]	Vapor sorption [%]
23 ± 2	5.88 ± 0.08	14.43
Secant modulus [MPa]	Yield stress [MPa]	
1276 ± 169	24.5 ± 2.6	

3.3.3. Stability testing

The long warfarin ODF was tested for its stability under different climatic conditions. The temperature was kept constant at 21 °C and two relative humidities were investigated. 60% relative humidity was chosen as standard storage condition according to ICH guideline Q1A [33], whereas 40% relative humidity was chosen as a storage condition under controlled conditions. The warfarin content and the mechanical properties were measured every four weeks to evaluate the drug and film stability over storage. Fig. 6 displays that the content of the investigated ODF showed no significant changes over twelve weeks of storage for 40% relative humidity ($p = 0.6255$) as well as 60% relative humidity ($p = 0.5139$). Yet, the AV of the samples stored at 60% relative humidity increased slightly due to rising standard deviations. With the highest AV of 10.1 the film was still below the threshold of the European Pharmacopoeia.

The investigation of the mechanical properties showed higher fluctuations that might be traced to the sensitivity of ODFs to ambient conditions during the measurements (Fig. 7). Already slight changes in the surrounding relative humidity would change the water content of the tested film (Fig. 8) leading to changes in the mechanical behavior because of the plasticizing effect of the incorporated water. The secant modulus showed no significant changes over twelve weeks of storage for both conditions ($p(40\%) = 0.5786$ and $p(60\%) = 0.5009$). The yield stress significantly increased at 40% relative humidity ($p = 0.0005$), which was not seen as disadvantage because the film resisted higher tensile stresses before starting to irreversibly deform. The yield stress at 60% relative humidity did not change significantly over twelve weeks ($p = 0.1330$).

3.4. Proof of concept in a tape dispenser

For a proof of concept, the produced long warfarin film of 2 cm width was coiled up on a spool. A commercial tape dispenser was equipped with the ODF holding spool to serve as a simple model (Fig. 9). It was feasible to coil up the long ODF without breakage of the film. Using the tearing mechanism of the tape dispenser it was possible to separate flexible lengths from the total film. The general concept of a long ODF and a dispenser could enable individualized therapy of films that could be performed by the patient himself or a caregiver at the point of care. Therefore, independent flexible dosing would be possible for the patient at home without a further production step to customize an initial product. An improvement of the tape dispenser regarding stability issues and dosing accuracy, however, is clearly necessary. It needs to be possible for the patient to dispense the correct dose that corresponds to a defined length of the film. Since the film has a defined width and thickness, the dose is only dependent on the dispensed length of the film piece. Furthermore, to clearly define the acceptable mechanical properties of the used ODFs, a final dosing device prototype would be necessary. The development of a dosing device for the flexible dosing of oral films is subject of further studies.

4. Conclusion

A long orodispersible film containing warfarin that is implementable for individualized therapy was successfully developed using a systematic approach for the formulation development. The viscosity of the polymer solutions and the mechanical properties of the dried ODFs turned out to be important characteristics for the development of a continuously produced long oral film. Concrete thresholds for the measurement values need to be obtained from tests with the dosing device to be used.

By developing a long orodispersible film that could be coiled up for the use in a cutting device, the first step in filling the gap pointed out by

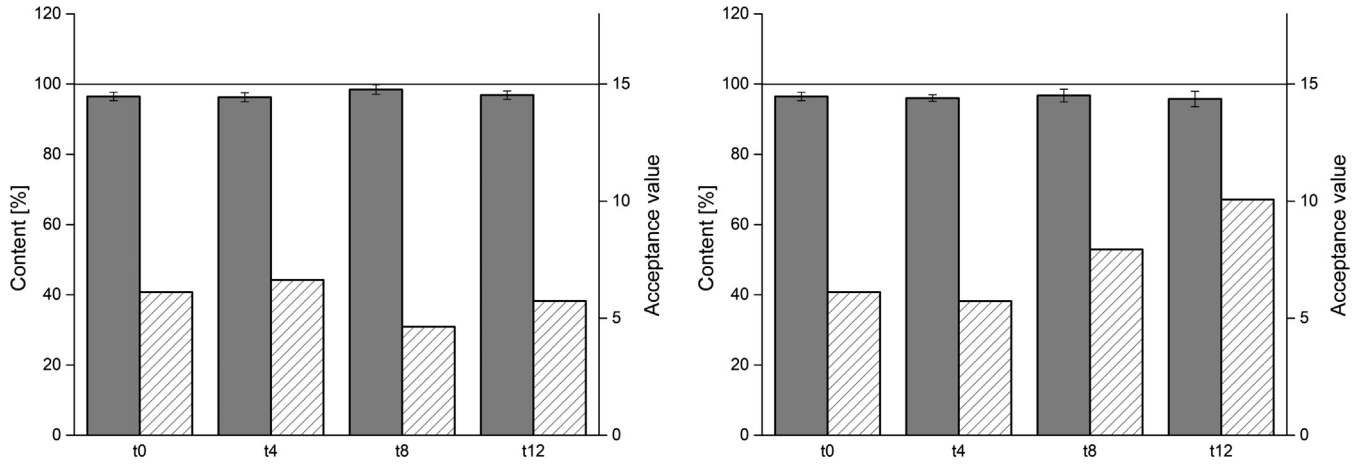

Fig. 6. Stability testing of warfarin sodium ODF. Left: 40% relative humidity; right: 60% relative humidity. API content referred to target value (filled columns) and acceptance value in accordance with Ph.Eur. 2.9.40 (dashed columns). The line represents content = 100% and acceptance value threshold = 15 (mean ± CI (α = 0.05), n = 10).

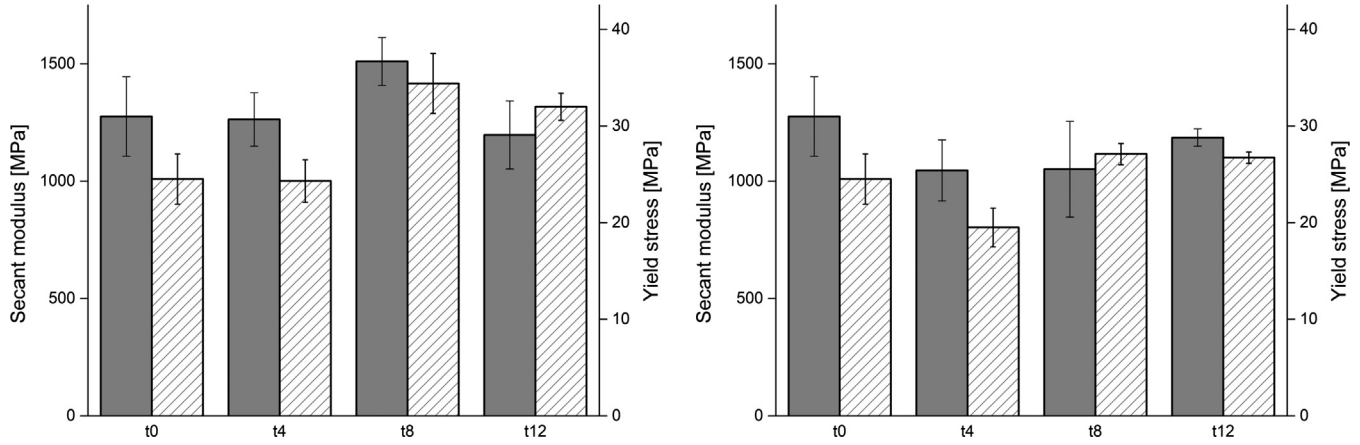

Fig. 7. Stability testing of warfarin sodium ODF. Left: 40% relative humidity; right: 60% relative humidity. Mechanical properties obtained from tensile test of the long ODF. Filled columns: secant modulus; dashed columns: yield stress (mean ± sd, n = 5).

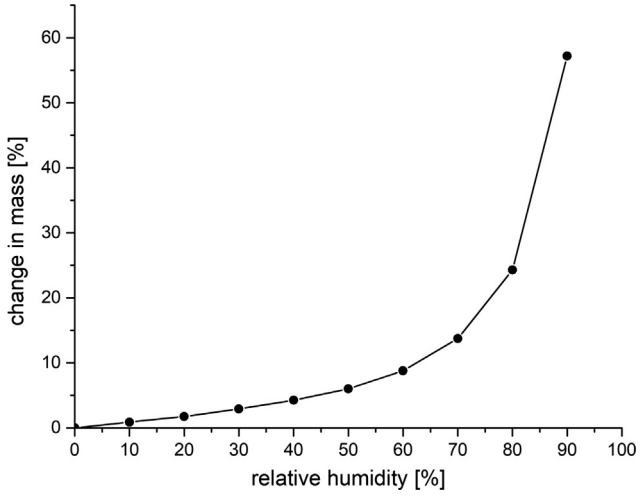

Fig. 8. Water vapor sorption isotherm of the long warfarin ODF (n = 1).

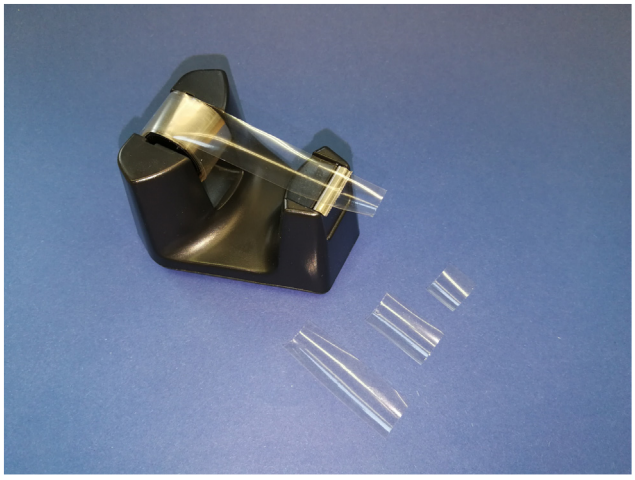

Fig. 9. Commercial tape dispenser equipped with the coiled-up warfarin sodium ODF and dispensed ODF samples in varying lengths.

Wening and Breitkreutz [17] was performed successfully. A solid dosage form that would enable individual and flexible dosing by the patient himself or a caregiver at the point of care was generated. The film could be easily cut without producing dust that often arose when splitting tablets. The stability test showed no loss in quality for the warfarin film over twelve weeks. While there is a lot of discussion about individualized medicine this work contributed a new solid dosage form containing the essential API warfarin for the flexible and safe dosing.

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Declaration of interest

The authors declare no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpb.2019.01.011.

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