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Research paper

SOFTs – Structured orodispersible film templates

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ABSTRACT

Orodispersible films (ODFs) have a high potential to accelerate the individualized medication. The films can be produced as drug-free templates and subsequently printed with an API (active pharmaceutical ingredient) solution or suspension according to the needs of the patient. While the printing technology already enables a precise dosing of fluids, there is still a high need of suitable, edible templates with elevated loading capacity. The structured orodispersible film templates (SOFTs) developed in this study should overcome this void. The SOFTs are pervaded with pores to realize a high API load into the film structure and possess a closed bottom side to prevent the printed fluids to pass through the film. They consist of a water-soluble cellulose derivative and are produced with the solvent casting method.

This study focused on the influence of the formulation of the film casting mass on the film properties, like porosity and disintegration time due to changed pore sizes and numbers. Due to the porous film structure a mass load of up to 6.1 mg cm^{-2} could be realized already in SOFTs, but, higher loads are feasible. The mechanical film properties could further be improved by additional matrix material in the suspension formulation, also inhibiting particle agglomeration and aggregation during the drying process, and positively influencing the dissolution behavior of the applied nanoparticles. An application of a protection layer on top of the loaded SOFTs improves the handling safety by inhibiting contact to the API and it prevents a removal of the particles from the film surface.

1. Introduction

The need to develop individualized solid dosage forms to realize a tailor-made medication for all age groups strongly increased in the last years. Especially children would benefit from this new medication because they develop from newborns to toddlers and infants and further to adolescents which requires a constant change of the applied API (active pharmaceutical ingredient) doses. So far, solid dosage forms like tablets or capsules have to be crushed or opened to receive lower API doses what can negatively influence the release properties [1]. This shows that conventional solid dosage forms are not suitable for an individualized medication [2]. An innovative technology that overcomes these issues are orodispersible films (ODFs). Thin, drug-free polymer templates are produced with technologies like solvent casting or hot-melt extrusion [3] and are loaded with APIs according to the needs of the patient. They disintegrate fast when placed in the mouth and release the API, where it is absorbed by the oral mucosa or swallowed into the stomach [4].

The drop-on-demand (DoD) technology is a promising method to load liquid API formulations on drug-free ODF surfaces [2,5]. Due to the high quality of the modern inkjet printing technology, uniform spaced and sized droplets can be created, which enables a precise drug load of the films [2]. API-containing suspensions and solutions which were formulated in water, ethanol or other organic solvents with different viscosities could already be applied onto ODFs [6]. The API concentration on the film can be adjusted to the needs of the patient by varying the drug concentration in the suspension or solution, adjust the size of the film administered to the patient or change the number of printing density and layers [7]. Furthermore, this printing technology enables the application of different API-containing suspensions or solutions onto one drug-free template, so the number of solid dosage forms can be reduced for the patient [8].

Besides the performance of the printing technology, the influences of the ODF substrate on the resulting film quality should not be neglected [5]. In previous studies, edible substrates as well as films from non-water soluble materials were used to investigate the behavior of the different printing technologies and performances of the inks. The applied substrates mainly differed in their structure: While films from various cellulose and starch derivatives as well as PET (polyethylene terephthalate) or further transparent materials possess a smooth

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surfaces, the film surfaces of icing sheets, rice papers and coated as well as uncoated papers are rougher and enable a better absorption of the applied fluid [2,6,7,9–12]. Sandler et al. indicated that the application of API containing solutions on a smooth PET foil results in a crystallization of the drugs on the film surfaces, while when printed on a structured paper substrate, the drug penetrates into it [2]. Furthermore, it was discovered that an absorption of the ink into the substrates minimizes the loss of the printed API amount due to a reduction of smearing effects on the surfaces and the thereby related insufficient application of the fluid on the film [10,12,13]. To further expand the absorption of APIs into the film matrix, Elele et al. [14] developed a polymer film made from HPMC (hydroxypropyl methyl cellulose) by freeze-drying which had a porosity of 95%. The porous film template was printed with ibuprofen and griseofulvin dispersions applied by the DoD technology and an imbibition of the drugs into the film structure was detected. Afterwards, the porous API carrier was encapsulated by a nonporous barrier film. Besides this, further freeze-dried films were developed from different materials like CMC (carboxymethylcellulose), sodium alginate or HPMC/wheat starch in order to load them with APIs or to compare the film properties to heat dried ODFs [15–17]. Liew et al. [15] detected a lower tensile strength for the freeze-dried films than for the heat dried ones. However, the films produced by freeze drying were faster disintegrating due to their better water uptake into the porous film structure. Furthermore, the drug release rates were higher for the freeze-dried films especially for high API loads [17].

Previous studies demonstrated that porous film substrates have great potential to be printed with API solutions or suspensions and to be applied to patients as individualized drug delivery systems [2,10]. As water-insoluble copy paper, for example, cannot be used as drug-free template in pharmaceutical applications and the production of freeze-dried film templates is quite expensive, a new, innovative porous substrate was developed in this study: Structured orodispersible film templates (SOFTs). SOFTs are drug-free templates, produced by solvent casting, the most common manufacturing route for ODFs. The films are pervaded by large pores and possess an open top side to load API containing suspensions or solutions into the film structure and one closed bottom side, so the applied fluids cannot permeate through the film (Fig. 2). Due to this structure, the API can be absorbed into the film and the large pores enable a high drug load. Besides this, no smearing effects occur during the API loading, not even if multiple printing layers are applied, because of the rough SOFTs surface permeated with pores. After the loading of the APIs into the SOFTs, a protection layer can be applied to prevent a direct contact of patients or healthcare professionals to the API during handling and to inhibit a possible removal of the particles from the films by mechanical stressing during further processing.

This study concentrates on the introduction of the SOFTs as well as the influence of the formulation of the film casting suspensions on film properties like film porosity, disintegration time and mechanical strengths. Furthermore, the loading of the SOFTs with a nanoparticle suspension is investigated. The SOFTs are loaded in various coating cycles with different suspension concentrations and the effects on film properties are characterized. Additionally, the formulation of the particle suspension is varied to investigate a possible improvement of the mechanical film properties and to prevent particle agglomeration and aggregation during drying, which is considered regarding the dissolution behavior of these SOFTs. This study is concluded with a closer consideration of the influences of the protection layer on the SOFTs disintegration behavior and mechanical properties.

2. Material and methods

2.1. Material

The structured orodispersible film templates were made from the HPMC (hydroxypropyl methyl cellulose) powder Pharmacoat®606 (kind grifts from Shin-Etsu Pharma and Food Materials Distribution GmbH, Germany and HARKE Pharma, Germany), x_{50} = 90 µm, which is easily soluble in water but very poorly soluble in ethanol. Hydroxypropyl cellulose (HPC, Sigma Aldrich, Germany) was added to the film casting formulation as binder. All suspensions were produced with denatured ethanol (95 vol-%, VWR International, Germany).

The drug-free porous templates were loaded with nanoparticular, ethanol-based suspensions consisting of the poorly soluble organic model compound Anthraquinone (Sigma Aldrich, Germany), initial particle size x_{50} = 25 µm, and the inorganic material Aluminum oxide, initial particle size x_{50} = 2.4 µm (Aeroxide® AluC, Evonic, Germany). Both materials were ground in a stirred media mill before applied onto the SOFTs. The organic particles were stabilized against agglomeration during milling with HPC and the resulting suspension formulated with Glycerol (Sigma Aldrich, Germany) and optionally with Vinylpyrrolidone-vinyl copolymer (KVA, Kollidon® VA 64, gift from BASF SE, Germany) before the loading onto the SOFTs. The Aluminum oxide suspension was stabilized with citric acid.

2.2. Production of SOFTs

In contrast to other ODFs, for which's manufacturing the matrix polymer is dissolved in the film casting mass, the SOFTs are produced from a particular suspension of HPMC. After the dissolution of the binder HPC in ethanol, HPMC particles are added and dispersed in the solution to form the film casting mass. This is degassed overnight and applied on a PET (polyethylene terephthalate) foil with an automatic film applicator coater ZAA 2300 (Zehntner, Switzerland). The casting speed was set at 10 mm s^{-1} and the gap height was 1000 µm. The films were dried in an oven at 50 °C for 30 min, removed from the substrate and stored airtight at room temperature.

2.3. Application of API and protection layer on SOFTs

The SOFTs were loaded with an ethanol-based suspension, so the structure of the films was not dissolved by the fluid and the applied particles are embedded into the film pores. Before the application onto the film, the Anthraquinone particles (c_m = 0.05 − 0.2) were ground with a stirred media mill (MiniCer, kind loan of Netzsch Feinmahltechnik GmbH, Germany) operated in circuit mode, until the target particle size x_{50} = 400 nm was achieved. The suspension was formulated against agglomeration with the non-ionic polymer HPC, c_{HPC} = 0.25 (referred to the solids content in the Anthraquinone suspension). The stirred media mill was operated with yttrium stabilized zirconium oxide (ZrO_2) grinding beads with an average diameter d_{GM} = 325 µm at a filling ratio ϕ_{GM} = 0.8. The stirrer tip speed was v_t = 9 m s^{-1} and the milling chamber as well as the storage vessel were cooled during the whole milling process (T_{cool} = 10 °C). Before loading the suspension onto SOFTs, Glycerol, c_{Gly} = 0.02 (referred to the suspension mass), was added to the organic formulation.

The SOFTs were additionally loaded with an Aluminum oxide nanosuspension (x_{50} = 100 nm), also ground in the stirred media mill. This suspension was electrostatically stabilized at pH 5 during milling.

The loading process of the SOFTs was performed with a specially designed and own built experimental setup, where a needle is moved in x- and y-direction over the film with a speed v_{load} = 220 mm min^{-1} and deposits a volume of 25 µl min^{-1} on the film surface (Fig. 1). The suspension was applied in a line pattern which covers a film area of 10 cm^2. Up to 5 coating cycles were applied on the SOFTs, while with every new cycle the suspension was placed in the gabs of the previous one. The films were dried at room temperature overnight.

A thin protection layer was sprayed on top of the particle loaded SOFTs to realize a polymer coating of 0.5 mg cm^{-2} on the films. It consists of a solution from the polymer HPC (c_{HPC} = 0.05) and ethanol. After the application the films were dried at room temperature.

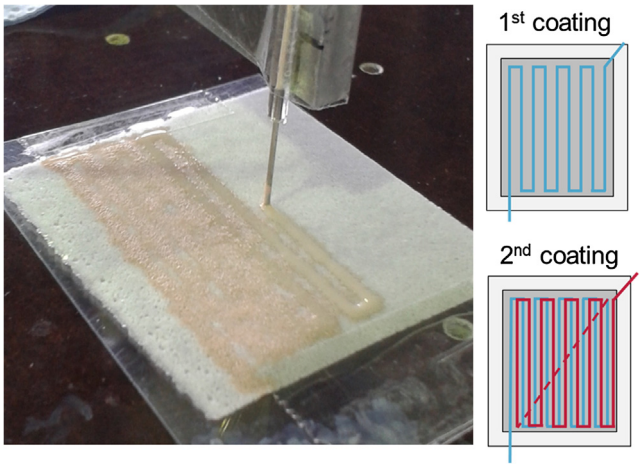

Fig. 1. Loading system and line pattern for application of suspensions on SOFTs.

2.4. Characterization methods

2.4.1. Characterization of suspensions

The viscosity of the film casting suspension was measured with a cone/plate system from Bohlin Gemini (Rotonelic Driver). The cone was 40 mm in diameter and had an angle of 4°. The samples were measured at a shear rate of $1\ s^{-1}$ at T = 25 °C.

The particle sizes of the Anthraquinone and Aluminum oxide suspensions were analyzed by dynamic light scattering (Nanophox, Sympatec). To guarantee a high-quality measurement, the suspensions were diluted. Aluminum oxide particles were diluted in ethanol, while a saturated Anthraquinone/ethanol solution was used for the organic model compound. Furthermore, the sizes of the particles redispersed from the Anthraquinone-loaded SOFTs were analyzed. A $2\ cm^2$ particle loaded sample was added to 0.9 ml distilled water and left to solve for 5 min until the film was completely disintegrated. Before the measurement, the particles were further diluted with a saturated Anthraquinone/water solution and the sizes were determined at T = 25 °C.

2.4.2. Characterization of SOFTs

The film thickness was measured with a digital gauge with an accuracy of 0.001 mm (Mitutoya Deutschland GmbH). A mean value was calculated from ten independent measurements placed over the SOFT.

Topographical analysis of SOFTs' structure were performed with a scanning electron microscope (SEM; EVO LS25, Zeiss AG) combined with an energy-dispersive X-ray spectroscopy (EDX; QUANTAX 400, Bruker Corporation) for element mapping in the cross section of the films. Images were acquired at 200 and 700-fold magnification.

The mechanical properties of the SOFTs were investigated with a materials testing machine (8136/20N, Zwick GmbH & Co. KG). The samples with a size of 5 × 35 mm were held between two grips and stressed with a speed of $5\ mm\ min^{-1}$. The maximum force, F_{max}, needed for the rupture of the SOFTs was recorded. The tensile strengths (F_{max} divided by the cross section area of the investigated film) of the SOFTs were calculated.

The theoretical porosity of the SOFTs was calculated according to Eq. (1), considering the volume of the film, V_{SOFT}, and its mass, m_{SOFT}, as well as the mean density, $\rho_{polymer}$, of the polymers, considering their shares processed in the SOFT:

$$\varepsilon = \frac{V_{SOFT} - \left(\frac{m_{SOFT}}{\rho_{polymer}}\right)}{V_{SOFT}} = 1 - \frac{\left(\frac{m_{SOFT}}{\rho_{polymer}}\right)}{V_{SOFT}} \quad (1)$$

The disintegration time was measured with the SFaB (slide frame and ball) method developed by Steiner et al. [18]. If not further mentioned, the films (3 × 4 cm) were fixed in the frame so the open pores of the SOFTs were at the top side of the device. The measurement was started when the ball (stainless steel, m_{ball} = 4 g, d = 10 mm) was placed on the first drop of 0.9 ml distilled water (T = 37 °C). After the start of the measurement, the rest of the water was placed on the film surface. The disintegration time is defined as the time the water needs to disintegrate the SOFT, allowing the ball to fall through the film. For better comparison, the specific disintegration time (measured disintegration time divided by the film thickness) was introduced.

The dissolution profile of the Anthraquinone-loaded SOFTs was investigated with the USP apparatus 2 (paddle apparatus) [19], combined with the "Punch & Filter" method, introduced by Krampe et al. [20] for the analyzation of ODFs. As dissolution fluid 1000 ml distilled water with a temperature T = 37 °C was used. A loaded SOFT (2 × 3 cm) was placed on the filter paper (MN 1674, Macherey-Nagel, Germany), so the particle-loaded side faced downwards, and the punch was placed on top of the film. To realize an appropriate wetting of the film, 0.5 ml distilled water (T = 37.5 °C) was pipetted on the SOFT each minute. Samples were taken from the dissolution medium every 2 min for the first 20 min. Afterwards, the time period was extended to 5 min until a measurement time of 50 min was reached and the sampling time was further extended to 10 min until the end of the experiment. The samples were filtered (syringe filter, 0.22 µm pore size) and analyzed with an UV–Vis spectrophotometer (UV-3100PC, VWR, USA). The concentration of all samples was below the saturation concentration of Anthraquinone in water.

3. Results and discussion

3.1. Theoretical approach and structure of SOFTs

The SOFTs were developed in order to create a highly porous, drug-free template for the individualized loading of API suspensions or solutions. For this purpose the ODF should have an open pore structure on the top side to enable a good loading of the APIs into the film, and a closed bottom side to circumvent leakage of the API-containing suspensions or solutions from the film during loading (Fig. 2). In order to maintain the porous film structure after the loading process and to realize a filling of the APIs into the film pores, an ethanol-based suspension or solution is applied. Due to the poor solubility of the matrix material (HPMC) in the organic solvent, the porous structure of the SOFTs is not dissolved during the loading of the API-containing fluids. After the application of the API on the structured films, a protection layer can be applied on top of the film surface to prevent a direct contact to the API during handling and to inhibit a removal of the API from the film surface due to mechanical stressing. Therefore, an ethanolic solution of the polymer HPC was sprayed on top of the particle-loaded SOFTs (Fig. 2). If taste masking is necessary, sweetening agents can be added to the solution.

To confirm the theoretical approach of the SOFTs structure, SEM images were taken from film cross sections (Fig. 3). These indicate that a side with open pores as well as a closed bottom side could be realized. Regarding the top side of the films, a porous film structure and open pores at its surface were detected (Fig. 31). The pores are supposed to be loaded with the API, enabling a high mass load of drugs into the film structure and preventing smearing effects of the suspensions or solutions during loading. It is also assumed that recrystallization effects during the drying of the API solutions could be reduced due to the high surface area in the SOFTs. The closed bottom side of the films show that a share of the binder was deposited there during the drying process, which leads to a barrier that a passing of the applied suspensions or solutions through the SOFT, even when higher fluid volumes were applied (Fig. 32).

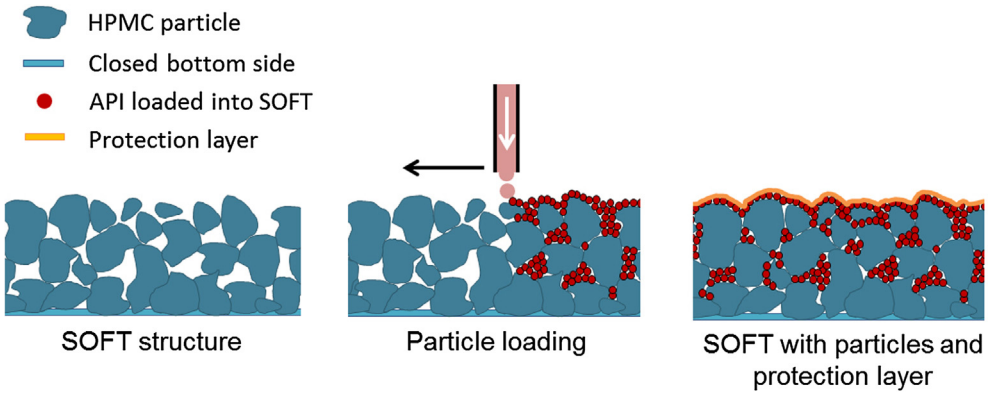

Fig. 2. Graphical description of SOFT structure, particle loading, and applied protection layer.

3.2. Influence of SOFT formulation

3.2.1. Particle-binder ratio

The film casting suspension of the SOFTs consists of ethanol as fluid as well as the polymers HPMC, applied as particulate matrix material, and HPC, used as binder. In the following the amount of the polymers (HPMC and HPC) in the suspension was investigated at a constant ethanol concentration (c_{EtOH} = 0.735). The concentration of the binder HPC, as share of the overall polymer content ($c_{HPMC+HPC}$ = 0.265) in the film forming suspension was varied between χ_{HPC} = 0.25 and 0.33. SEM images of film cross-sections identified a change in film thickness and structure with different HPC polymer shares (Fig. 4). In parallel the particle concentration (HMPC) in the formulation decreases with increasing HPC contents. This results in thinner SOFTs with smaller pores pervading the film, because the high binder amount in the formulation does not only cover the surfaces of the HPMC particles, but also fills the pores of the SOFTs. A reduction of the HPC share to χ_{HPC} = 0.31 and 0.28 in the film casting suspension increased the particle amount in the formulation, resulting in higher film thicknesses with more open pores pervading the SOFTs. A further decrease of the binder concentration (c_{HPC} = 0.25) resulted in brittle and badly workable SOFTs with large pores and no closed side due to the lack of binder between the HPMC.

As a consequence of changes in the SOFTs microscopic structure by varying the binder amount, the specific disintegration times as well as the tensile strengths were clearly influenced. Regarding the specific disintegration times, an increase could be detected for higher binder concentrations (Fig. 5). With an increase in the HPMC content, the numbers of pores in the SOFTs as well as their sizes increase. At the beginning of the measurement, the water was placed onto the open, porous surface of the SOFTs. The water better penetrates into the film structure when the HPC content is smaller, resulting in lower specific disintegration times.

The highest tensile strengths were obtained with a binder share of χ_{HPC} = 0.33 in the film forming suspension (Fig. 5). Due to the high amount of binder in the suspension, a dense film structure was achieved after the evaporation of the solvent (see Fig. 4). With decreasing binder concentrations the tensile strength of the SOFTs decreases, indicating that the mechanical strengths of the films were weakened due to the increasing pore sizes and numbers pervading the films. Furthermore, for very small binder shares, χ_{HPC} = 0.25, no closed side of the films was obtained, additionally decreasing the tensile strengths.

In order to achieve the desired properties of the SOFTs, a compromise between low specific disintegration times and high tensile strengths combined with large pores must be met. In order to realize these requirements, a binder share of χ_{HPC} = 0.28 (c_{HPC} = 0.0754, mass concentration referred to film casting suspension) regarding the overall polymer amount of the film forming suspension was chosen for the further investigations.

3.2.2. Ethanol concentration in suspension

Besides the binder share, the ethanol amount in the film casting suspension influences the properties of the SOFTs. Investigations proved than an ethanol concentration between c_{EtOH} = 0.702 and 0.745 resulted in high-quality SOFTs. Ethanol contents smaller than c_{EtOH} = 0.710 led to a high increase in the viscosity of the film forming suspension (Fig. 6). Due to the film thickening properties of the solved binder HPC and the high HPMC particle content, the viscosities increased over 100 Pas ($\dot{\gamma}$ = 1 s^{-1}) and complicated the film casting due to the poor flow properties of the film casting suspension. Accordingly, films produced with these suspensions had high film thicknesses and large standard deviations due to uneven film surfaces. With ethanol concentrations higher than c_{EtOH} = 0.710, the viscosity decreased below 60 Pas, which enabled a good flowability during film casting and led to thinner film thicknesses because of the reduced polymer content and the improved arrangement of particles in the suspension due to the lower viscosities. An ethanol concentration higher than c_{EtOH} = 0.725 resulted in no further decrease of the film thicknesses, although suspension viscosities further decreased. It is assumed that this is caused by

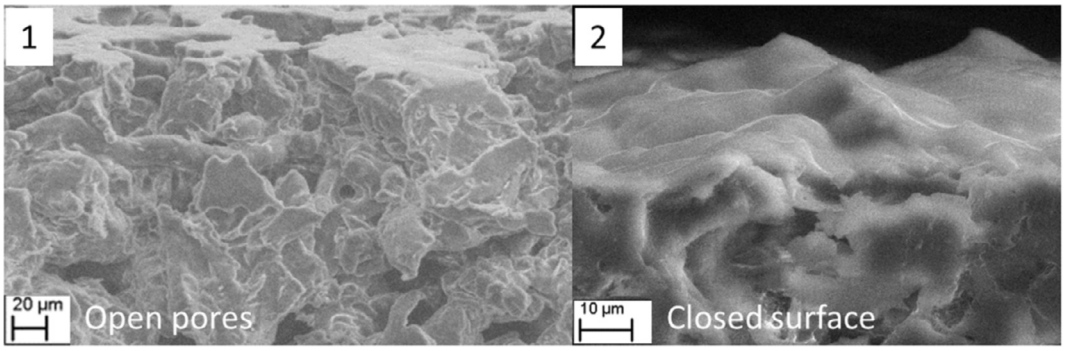

Fig. 3. SEM images of closed surface and open pores of SOFTs.

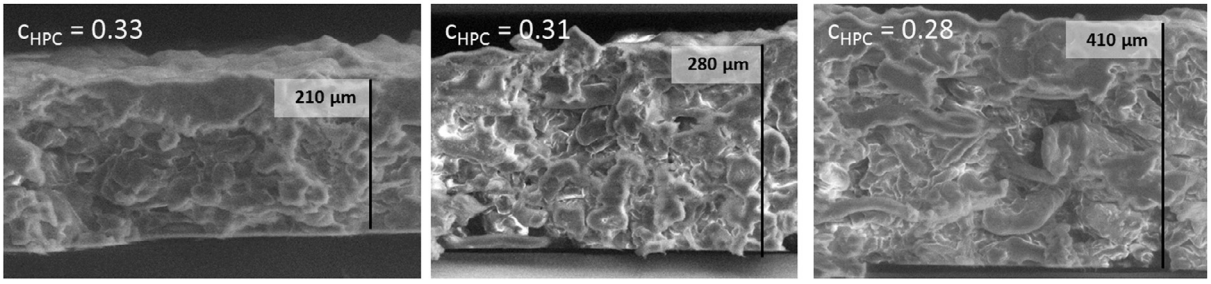

Fig. 4. SEM images of SOFT cross sections with varying binder concentration.

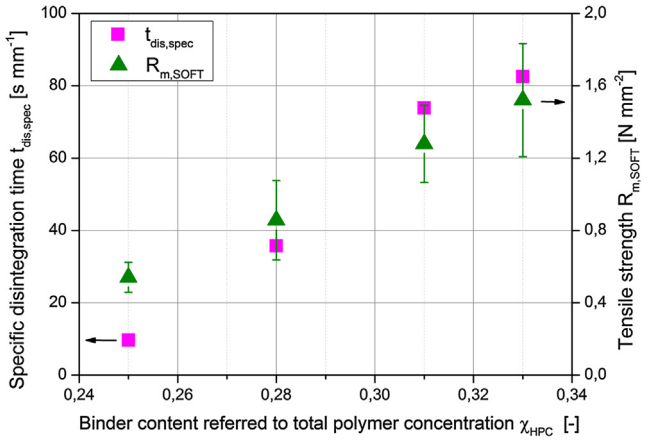

Fig. 5. Influence of binder content on specific disintegration time and tensile strength, n = 3–4.

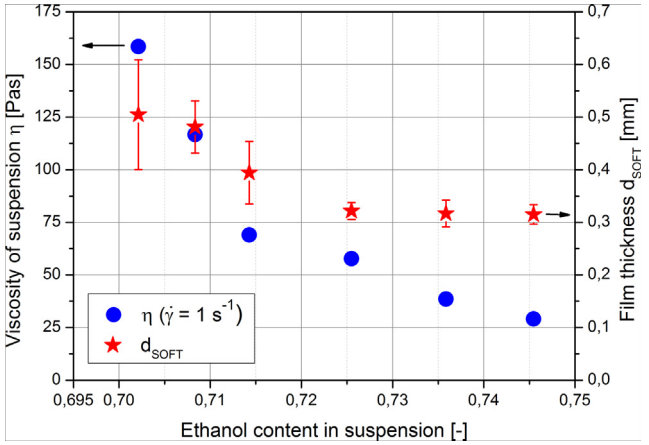

Fig. 6. Influence of ethanol content on suspension viscosity and SOFT thickness, n = 10.

the good flowability of the film casting suspensions. Due to the still high viscosities (larger than η = 25 Pas) of the film casting suspension it can be assumed that the particles as well as the binder are homogeneously dispersed in the suspension during casting and no sedimentation effects occur. During drying, the ethanol evaporates, the particles get in contact with each other and the structure of the SOFTs is developed. Due to the appropriate flowability of these suspensions (smaller than 60 Pas) a homogeneous film surface was generated, what resulted in a low standard deviation. Furthermore, the large particles in the suspension hinder the particles to form a denser package, so only low changes in the film thicknesses were obtained for the film casting masses with an ethanol concentration above c_{EtOH} = 0.725.

Fig. 7 indicates that the specific disintegration time of the SOFTs is almost not influenced by the ethanol concentration in the film casting

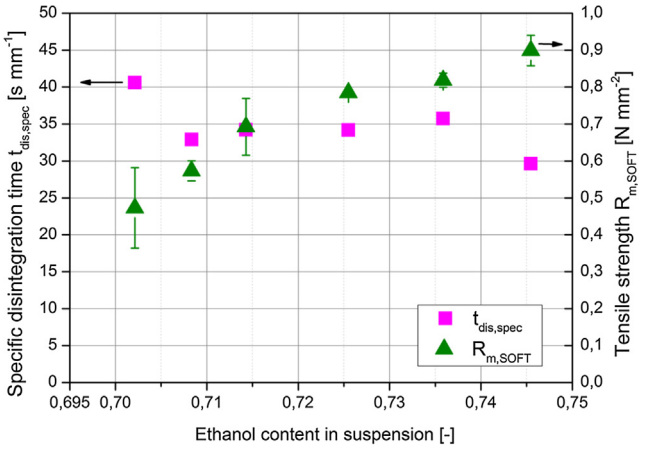

Fig. 7. Influence of ethanol content in the suspension on the specific disintegration time and the tensile strength, n = 3–4.

suspension. Only the films produced with the highest (c_{EtOH} = 0.745) and the lowest (c_{EtOH} = 0.702) ethanol content in the suspension differ from the other specific disintegration times. It is assumed that the specific disintegration time was a bit lower for c_{EtOH} = 0.745 because the thickness of this film was slightly less than for the SOFTs with an ethanol concentration c_{EtOH} = 0.725 and 0.735. This resulted in faster disintegration times than for samples with ethanol concentrations between c_{EtOH} = 0.708 and 0.735. The specific disintegration time of the SOFT cast from the suspension with the lowest ethanol content c_{EtOH} = 0.702 showed the longest disintegration behavior. It is assumed that, when the water was placed on the top of the film, not all pores could be filled down to the bottom of the SOFT due to its high and inhomogeneous film thickness. Thus, the water had to solve the upper film layers first, before it reached the bottom of the SOFTs, resulting in the disintegration of the whole film.

A stronger dependency on the ethanol concentration in the film casting suspension was detected for the tensile strength of the films. A higher mechanical strength was detected for SOFTs with a higher ethanol concentration in the formulation. It is assumed that this is caused by the longer drying times of the SOFTs containing more ethanol in the film casting suspension and the resulting better rearrangement of the particles and better distribution of the binder, e.g. in the contact area between particles and the closed side of the film. With lower ethanol concentrations and therewith higher suspension viscosities, the binder could not migrate in the sample during drying, resulting in a thinner polymer layer at the closed side of the SOFT, indicated by a lower tensile strength. Therewith, the mechanical properties of the SOFTs were improved with ethanol concentrations higher than c_{EtOH} = 0.725, were the binder accumulates at the top side of the film.

In order to guaranty good handling properties of the film casting suspension and good mechanical properties of the SOFTs, an ethanol concentration of c_{EtOH} = 0.735 was chosen as standard formulation.

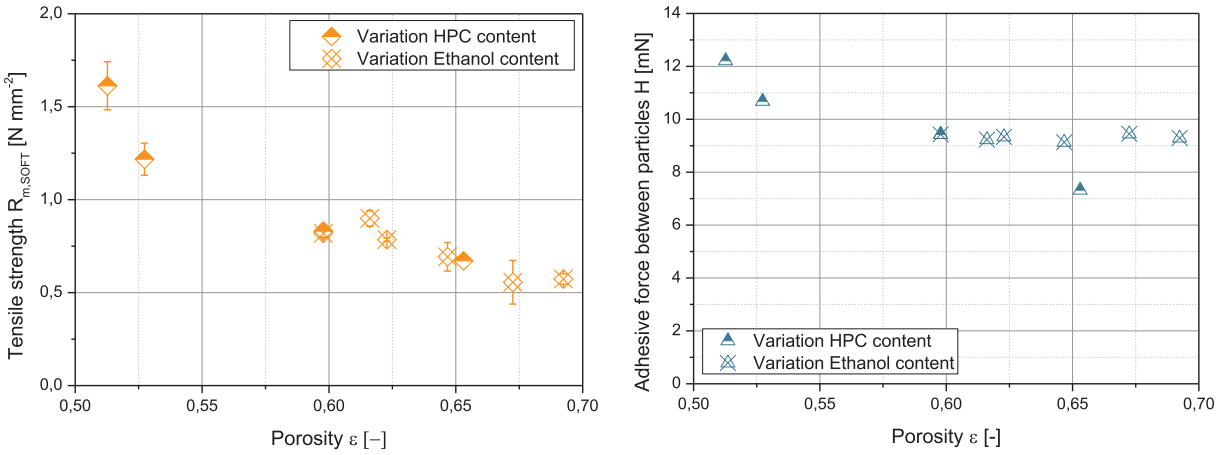

Fig. 8. Influence of SOFTs porosity on the tensile strength (left) and adhesive forces (right) considering different suspension formulations.

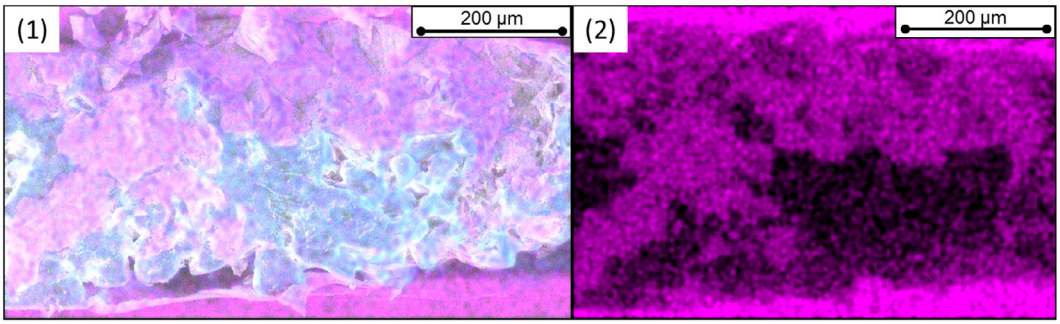

Fig. 9. SEM/EDX images describing the application of Al_2O_3 particles into the pores of the SOFT; (1) EDX detection of elements Al, O and C; (2) EDX detection Al.

3.3. Influence of porosity on mechanical properties

The theoretical porosity of the SOFTs (calculated according to Eq. (1)) could be influenced by the variation of the binder and ethanol concentration in the film forming suspension. While a high porosity is favorable to realize a high mass load of API into the film, a negative effect on the mechanical properties was detected (Fig. 8, left). The increase in the porosity indicated a decrease in the tensile strengths of the SOFTs, while the suspension formulation does not considerably influence the mechanical film properties. Low porosities in the films were achieved with a high binder amount in the film casting suspension to realize a good linkage between the HPMC particles and a thick polymer layer at one side, resulting in higher tensile strengths of the films. Furthermore, the higher binder amounts in the casting formulation could also lead to smaller and less pores in the film. Regarding SOFTs with higher porosities, the tensile strengths decrease to $R_{m,SOFT} = 0.5\,N\,mm^{-2}$ for films with a porosity $\varepsilon = 0.66$ or higher, indicating a low connectivity between HPMC particles resulting in brittle films. This showed that with a higher porosity the pores pervade the film and provide a large cavity volume which can be loaded with API suspensions or solutions, although the tensile strengths of these films are low. However, loading the pores increases the strength of the films as shown later.

Besides the tensile strength, the adhesive forces between the particles, H, were calculated for the SOFTs based on the Rumpf equation (Eq. (2)) with which the forces of solid contacts between the HPMC particles can be calculated [21]. The particle morphology of the HPMC was estimated to be spherical with no size distribution.

$$H = \frac{8}{9} * R_{m,SOFT} * d_{HPMC}^2 * \frac{\varepsilon}{1-\varepsilon} \quad (2)$$

Regarding the adhesion forces between the particles for different HPC contents a decrease can be detected with higher porosities, which resulted from the lower binder content in the suspension formulation (Fig. 8, right). Thus, the increase of the HPC concentration led to higher adhesive forces between the HPMC particles indicating a stronger connection of the particles in the SOFTs structure. The variation of the Ethanol content in the formulation does not influence the adhesion forces between the particles of the matrix material due to the constant particle-binder ratio in the formulations.

The SOFTs chosen for the further investigations in this study had a theoretical porosity of $\varepsilon = 0.59$.

3.4. Loading of SOFTs with suspension

The loading behavior of nanoparticles into the SOFTs structure was topographically analyzed by means of SEM images and element mapping (EDX). In order to distinguish the organic SOFT materials and the nanoparticles by EDX, an Aluminum oxide nanosuspension ($x_{50} = 100$ nm) was applied onto the film and the cross section of the loaded SOFT was analyzed. In Fig. 9(1) the film cross section is shown detecting the distribution of the elements Al, O and C in the films cross-section loaded from the top side. While the elements O (Oxygen, blue) and C (Carbon, green) in the SEM/EDX images indicated the film matrix (HPCM and HPC) in particular, the pink color showed the distribution of the element Al (Aluminum). For a better identification of the Alumina allocation in the cross-section, Fig. 9(2) shows only the Al located in the SOFTs. The SEM/EDX images confirmed that a loading of the particles into the film pores is possible and that the suspension pervades through the SOFT, down to the closed side of the film. Furthermore, it could be observed that the porous film matrix was not dissolved during the loading of the SOFTs, caused by the application of an ethanol-based suspension.

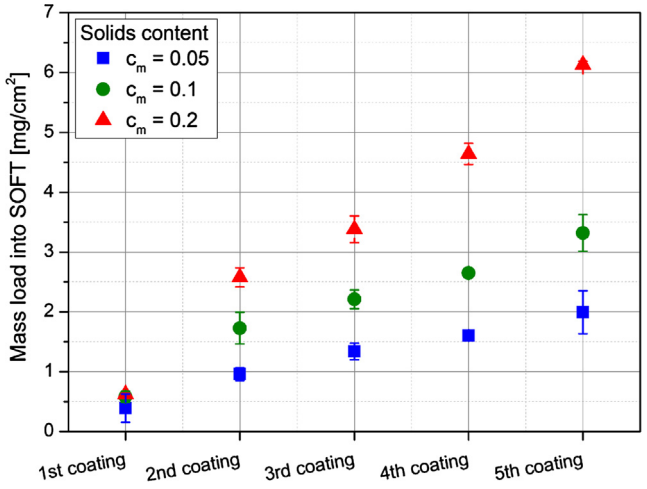

Fig. 10. Variation of solids content of Anthraquinone suspension and coating cycles; n = 3.

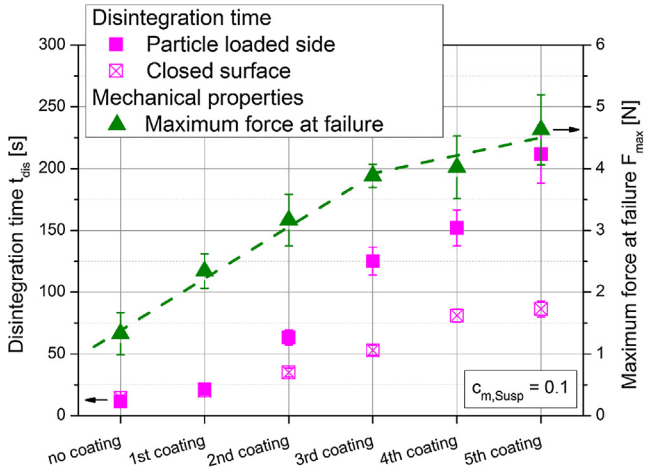

Fig. 11. Influence of coating cycles (c_m = 0.1) on disintegration time and maximum force before failure of SOFT; n = 4.

3.4.1. Variation of coating cycles and particle concentration

The realization of a wide range of drug loads on the SOFTs is necessary to provide flexible individualization of this solids dosage form. For this purpose, the individual drug dose can be realized by the adjustment of either the coating cycles or the solids contents of the suspension (x_{50} = 400 nm) to the patients' needs. In this study, suspensions were applied onto the film surface with the experimental setup shown in Fig. 1. It could be detected that with an increase in coating cycles, the mass load applied on the SOFTs was increased for all nanoparticular suspensions (c_m = 0.05 − 0.2) (Fig. 10). Furthermore, the highest mass load m_{SOFT} = 6.1 mg cm^{-2} was realized with the solids content c_m = 0.2 in the Anthraquinone suspension with 5 coating cycles. The mass load m_{SOFT} measured in these experiments considers the increase in weight of the SOFTs after the application of the suspension on the films and subsequent drying. As the suspension consists of the Anthraquinone particles and HPC (for the stabilization against agglomeration during milling) the maximum particle load, $m_{SOFT,Anth}$, onto the SOFTs (c_m = 0.2, 5 coating cycles) was $m_{SOFT,Anth}$ = 4.9 mg cm^{-2}. Considering an ODF with a standard size of 6 cm^2, dose of approx. up to 30 mg can be applied to the patient with one SOFT.

The integration of particles into the SOFTs structure influenced the disintegration time as well as the maximum force before failure of the films. Considering the disintegration time of the SOFTs loaded with an Anthraquinone suspension c_m = 0.1, two different measurement setups were used: (1) application of the water and ball onto the porous, particle loaded side, as described before, and (2) application onto the closed, bottom side of the film. An increase in the disintegration time was detected with higher particle loads, independent of the measurement setup (Fig. 11). Regarding the disintegration times were the applied liquid was placed onto the particle loaded, porous side of the SOFTs, the times increase more than 10-fold between the 1st and the 5th coating layer, reaching 200 s for 5 layers. The increase in the particle load on the SOFTs inhibited the access of the water to the soluble polymer matrix of the films and therewith extended the disintegration of the films. Furthermore, it is assumed that the wetting of the surface of the film was decelerated due to the hydrophobic properties of the loaded particles. The disintegration times analyzed by wetting the closed, unloaded side of the SOFTs, indicated shorter disintegration times. This clarified that after the wetting and dissolution of the closed polymer layer of the film, which is assumed to take the same time period for all SOFTs, the particle amount applied into the film further delayed the disintegration. Due to the increased particle concentration in the film, the water could not pass through the pores but had to dissolve the film matrix as well as the additional HPC applied with the loaded suspension and, therewith, the disintegration times extended. Caused by the better access of the water to the soluble polymer, the disintegration times were shorter than 100 s for all samples and could be reduced by more than 50% compared to the films desintegrated at the particle loaded side.

The mechanical properties of the particle loaded SOFTs were described by the maximum force before failure of the loaded films. The increase in coating cycles improved the mechanical properties of the SOFTs, achieving a mechanical force over F_{max} = 4.5 N at 5 coating layers. Due to the loading of the suspension, containing Anthraquinone particles and HPC, the pores of the SOFTs were filled and therewith, the HPMC particles were additionally linked to each other while the porosity of the films decreases. In particular, this better connection of the HPMC particles could be detected during the first three coating cycles were the pores of the SOFTs are filled with particles and the porosity of the films decreased, resulting in a linear growth of the maximum force before failure. Afterwards, the particles were more likely applied on the SOFTs' surface, resulting in a lower increase of the mechanical strengths of the films.

3.4.2. Influence of loading suspension formulations on final SOFTs properties

As already stated, the suspension applied onto the SOFTs has an influence on the mechanical strengths of the loaded films. As good mechanical film stabilities were achieved with a high number of coating cycles, a potential was identified to further improve mechanical strengths for films with lower coating cycles by optimizing the suspension formulation. For this purpose, the polymer concentration in the Anthraquinone suspension was increased. Therefore, KVA was added to the ethanol-based Anthraquinone suspension (c_m = 0.1) already containing 25 wt-% HPC (c_{HPC} = 0.25, referred to the solids content of the suspension) which was added to the suspension to stabilize the particles during milling. Thus, the polymer concentration in the suspension was varied between c_{Poly} = 0.25, without addition of KVA, and c_{Poly} = 0.75, addition of 50 wt-% KVA (referred to the solids content of the suspension). The SOFTs were loaded with these suspensions in two coating cycles and the maximum forces at failure of the films were characterized (see Table 1). A clear increase in the maximum force could be detected with increasing polymer concentrations in the suspensions. Due to the additional polymer solved in the suspension, the linkage of the HPMC particles was improved with the increased polymer amount. The mechanical strengths could be increased from F_{max} = 3.1 N (c_{Poly} = 0.25) to F_{max} = 4.6 N with c_{Poly} = 0.75. Although the polymer concentration was increased by 50% in the suspensions, the particle amount applied onto the SOFTs did not decrease drastically (Table 1).

Table 1
Influence of suspension formulation on mechanical strength and particle size after film redispersion and calculation of particle concentration in the suspensions, according to [22].

Addition KVA	Maximum force at failure F_{max} [N]	Particle concentration in suspension V_{Anth} [%]	Particle sizes after film redispersion x_{50} [nm]
SOFT	1.3 ± 0.3	–	–
c_{Poly} = 0.25	3.1 ± 0.4	6.43	1217.5
c_{Poly} = 0.35	3.5 ± 0.1	6.29	1025.6
c_{Poly} = 0.50	3.7 ± 0.1	6.22	766.4
c_{Poly} = 0.60	4.0 ± 0.1	6.18	579.0
c_{Poly} = 0.75	4.6 ± 0.2	6.12	458.1

The reason for this is the volume dosing of the application device. While the polymer was solved in ethanol, the share of the particles in the suspension per volume fraction was not substantially influenced.

Nanoparticles are applied in pharmacy to improve the bioavailability of poorly water-soluble APIs. One of the main targets of processing nanoparticle suspensions to solid dosage forms is the preservation of the particle sizes and, therewith, their improved dissolution rate in water. Anthraquinone suspension only stabilized with HPC (c_{Poly} = 0.25) directly applied on the film showed a drastic increase in particle size after film redispersion of up to x_{50} = 1217 nm (Table 1). With higher polymer concentrations in the suspensions, the particle sizes decrease down to x_{50} = 458 nm for c_{Poly} = 0.75. This is caused by the additional matrix material applied to the Anthraquinone particles by the coating cycles, which prevent an agglomeration and aggregation during drying. KVA acts as an additional matrix forming agent to embed and separate the Anthraquinone particles.

Besides the analyzation of the particle sizes, an improved release rate with higher polymer amounts in the loaded Anthraquinone suspension was shown in the dissolution behavior of the SOFTs (Fig. 12). Although the dissolution profile of the investigated SOFTs differed only slightly until 70% Anthraquinone was released, the longest dissolution times were detected for SOFTs loaded with the Anthraquinone suspension containing c_{Poly} = 0.25. Regarding the times needed to release 90% of the Anthraquinone loaded on the SOFTs, a clear decrease was detected for higher polymer concentrations in the suspension. Hence, a two-fold increase in polymer concentration in the suspension reduces the dissolution time $t_{Anth,0.9}$ by almost 33%.

This demonstrated that besides the improvement of the mechanical film properties with higher polymer concentrations in the suspension, the agglomeration and aggregation of the particles can almost be inhibit resulting in an improved release rate, while the particle dose applied

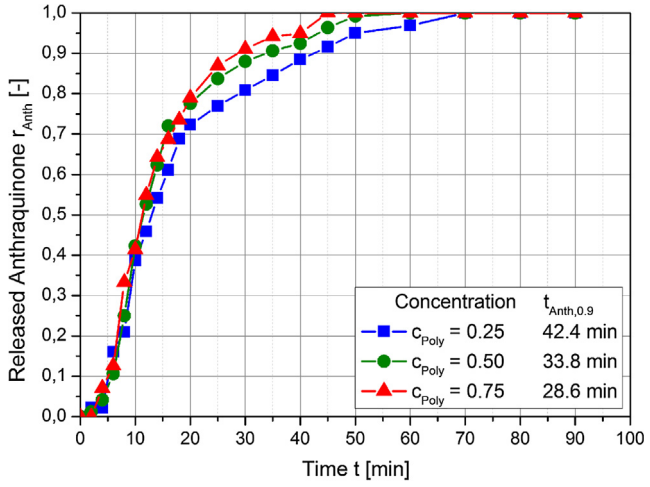

Fig. 12. Dissolution profile of SOFTs loaded with Anthraquinone suspensions containing different polymer concentrations.

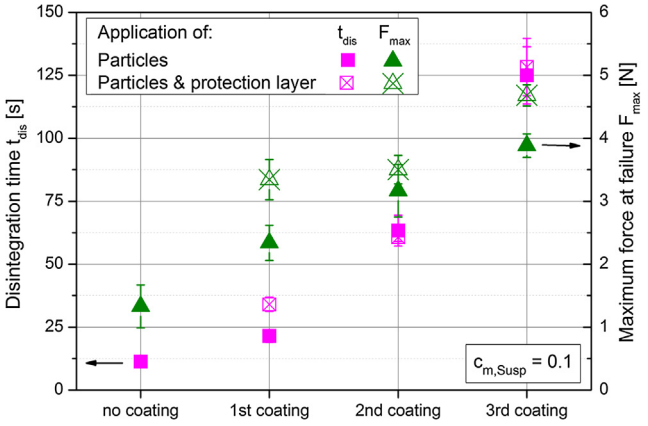

Fig. 13. Effect of protection layer on disintegration time and mechanical strength of SOFT with varying coating cycles.

onto the SOFTs was not drastically reduced and can be adjusted with coating process parameters.

3.5. Application of a protection layer

To avoid the direct contact of healthcare professionals and relatives to the nanoparticular API applied on the SOFTs as well as to prevent a removal of the API due to mechanical stressing, a protection layer containing HPC was applied on the particle loaded SOFTs surface (Fig. 2). In addition to these advantages considering the handling of the SOFTs, it is assumed that the protection layer could also have a positive influence on the storage behavior of the particle loaded SOFTs by reducing the diffusion to the film surface and thus, direct contact of the API to e.g. the humidity.

The application of a further layer only slightly influenced the disintegration time of the SOFTs (Fig. 13). While the disintegration time of the films loaded with one coating cycle showed the highest increase (Δt_{dis} = 13 s), the influence could be neglected for a high number of cycles. Furthermore, the protection layer on the particle-loaded SOFTs increased the maximum force at failure of the films, independent of the coating cycles. Thus, the additional polymer applied on the top of the films formed another thin layer which led to a better linkage between the HPMC particles and an additional strengths.

4. Conclusion

Structured orodispersible film templates are newly developed drug-free ODFs which enable an application of API suspensions or solutions directly into the porous film structure. The film can be manufactured with the solvent casting method and consists of one side with an open, porous structure enabling the infiltration and loading of suspension into the SOFTs and one closed side hindering the applied liquid to pass through the film. By these feature a maximum of loading capacity and application safety is achieved.

The properties of the SOFTs can be adjusted by formulation variation of the film casting suspensions. Thereby, the binder concentration referred to the particles amount as well as the ethanol content in the film casting suspension influence the mechanical film properties, the film porosity and the disintegration times of the SOFTs. Furthermore, a relation between the film porosity and the tensile strength was obtained, independent of the formulation of the casting suspension. The application of an ethanol-based nanosuspension into the porous SOFTs structure enabled a mass load of up to 6.1 mg cm^{-2} with a solids content of Anthraquinone suspension c_m = 0.2 and 5 coating cycles. The load of the pores in the SOFTs with the suspension results in an increase in mechanical strength which can be further increased with the addition of the polymer KVA as matrix material in the coating suspension.

The higher polymer amount additionally decreases particle agglomeration and aggregation during the drying process, resulting in a faster release of Anthraquinone when dissolved in water.

To avoid the direct contact between the nanoparticulate API and patients or healthcare professionals as well as to prevent a removal of API particles due to mechanical stressing, a protection layer was applied on top of the API loaded films. This polymer layer additionally improved the mechanical strength of the particle loaded SOFTs, while the disintegration times were not further increased.

The new development enables an improvement in individualized medication. Due to the rough, open surface and the high porosity of the SOFTs the potential API load is drastically increased compared with conventional closed-surface ODFs. Additionally, an application of API suspensions and solutions without smearing effects is achieved and particle loads up to 30 mg can be printed onto a standard sized ODF (6 cm^2), expanding the applicability of this individualized solid dosage form to less potent APIs and a wide range of API doses that can be printed on the SOFTs. The simple manufacturing of the SOFTs with a solvent casting method and the unique structure of the films provide the possibility to further forward the individualized medication by printing tailor-made doses of one API or combinations of multiple APIs onto SOFTs.

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