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Increased drug load and polymer compatibility of bilayered orodispersible films

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ABSTRACT

The addition of enalapril maleate to a casting solution for orodispersible films (ODFs) containing hypromellose and carbomer 974P as film forming agents (standard casting solution, SCS) caused a dose dependent reduction of the viscosity. This phenomenon was a serious problem in the preparation of ODFs with an increased enalapril load (> 1 mg per ODF) when using the solvent casting method.

The aim of the present work was twofold. Firstly, the influence of enalapril on the viscosity of SCS was studied in more detail. Secondly, two methods for increasing the enalapril load of an ODF were investigated that did not negatively influence the properties of SCS. The casting height was increased and the preparation of bilayered ODF, using the double-casting method, was explored. In the framework of the bilayered ODFs the compatibility between the film forming agents hydroxypropyl cellulose (HPC), sodium alginate (SA), hydroxyethyl cellulose (HEC) and the combination hypromellose–carbomer 974P (SCS) was investigated.

Results and conclusions: We found that enalapril concentration dependently reduced the pH, thereby negatively influencing the gel formation and the viscosity of SCS.

An increased casting height did not result in a proportionally increased enalapril load.

The enalapril load could be doubled when a bilayered ODF containing two layers of SCS was produced.

Finally, not all combinations of film forming agents could be used for the preparation of bilayered ODFs. Besides, the sequence in which the different polymer layers were casted affected the appearance of the ODFs. In conclusion, the best formulations were produced with the polymer combinations SCS/SCS and SCS/HPC.

1. Introduction

Orodispersible films (ODFs) are a relatively new oral dosage form. An ODF is a thin single- or multilayer sheet that disperses rapidly when placed on the tongue (European Pharmacopoeia 9th edition). For small scale extemporaneous preparation of an ODF the solvent casting method is the production method of choice. This method comprises dissolution or dispersion of the active pharmaceutical ingredient (API) in a suitable casting solution that is subsequently cast and dried (Hoffmann et al., 2011).

A serious drawback of ODFs as dosage form is the limited drug load that can be applied. Therefore, only potent APIs can be used so far (Borges et al., 2015; Hoffmann et al., 2011; Krampe et al., 2016).

Theoretically, the drug load of an ODF can simply be increased by adding more API to the casting solution. This, however, may lead to crystallization of the API in the final dosage form after evaporation of

the solvent and/or upon storage, thereby affecting the physical properties of the product (e.g., the mechanical strength and dissolution rate). In case the amount of API added to the casting solution exceeds its solubility, the API no longer is dissolved but will become dispersed. This may yield ODFs with a gritty surface which is unfavourable in terms of patient acceptance. Furthermore, it may negatively influence the properties of the casting solution, the uniformity of mass, uniformity of content, disintegration time, and the mechanical properties of the ODF (Hoffmann et al., 2011; Kianfar et al., 2012; Upreti et al., 2014; Visser et al., 2015a, Woertz and Kleinebudde, 2015).

The drug load of an ODF can also be enhanced by increasing its size and thickness. This, however, may result in thick and brittle films, with a negative influence on patient compliance and thus on the therapeutic outcome.

Another approach to achieve an increased drug load is by printing of the API. Different printing techniques have been described in literature,

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e.g. (thermal) inkjet printing, flexographic printing and 3D printing (Genina et al., 2012; Janßen et al., 2013; Sandler and Preis, 2016). Buanz et al. explored thermal inkjet printing for creating personalized-dose API on a plain edible film (Buanz et al., 2011). The different printing techniques are suitable for the extemporaneous preparation of oromucosal films (including ODFs) in an industrial setting as well as in a (hospital) pharmacy (Sandler and Preis, 2016; Schroedl et al., 2011).

A further possibility for increasing the drug load may be the application of a bilayered (or multilayered) ODF. Research on bilayered or multilayer films so far focuses on buccal films or sublingual bilayered films and not yet on ODFs (Borges et al., 2015; Juliano et al., 2008; Preis et al., 2014). In buccal films the use of different types of layer may lead to uni-directal drug release, controlled drug release, better mucoadhesive properties, and it may influence the disintegration time (Juliano et al., 2008; Preis et al., 2014).

For ODFs the use of two or multiple layers may serve a different goal. It is known that some APIs, especially enalapril maleate, in higher doses negatively influence the characteristics of the casting solution, making it unsuitable for casting (Visser et al., 2015a). In that case a bilayered film produced with two lower drug load containing layers may offer a solution.

The aim of the present study is twofold. Firstly, the influence of an increased drug load on the properties of a casting solution is profoundly investigated. Enalapril maleate (further referred to as enalapril) is used as model drug. The used casting solution was developed in a previous study and contains hypromellose and carbomer 974P as film forming agents (Visser et al., 2015a). This particular casting solution is further referred to as the standard casting solution (SCS).

Secondly, two methods yielding higher drug loads of the ODFs without influencing the properties of the SCS were investigated: the application of an increased casting height and the preparation of a bilayered ODF. For the latter, the compatibility of different polymers was tested in order to gain a better understanding of the possibilities to produce bilayered ODFs.

2. Material and methods

2.1. Materials

Enalapril maleate was obtained from Fagron, Capelle aan den IJssel, The Netherlands.

Hypromellose (HPMC, Methocel E3 premium LV, a gift from Colorcon, Kent, UK), hydroxypropyl cellulose (HPC), sodium alginate (SA, Sigma-Aldrich, St. Louis, USA), hydroxyethyl cellulose (HEC, Genfarma, Maarssen, The Netherlands) and carbomer 974P (Bufo, IJsselstein, The Netherlands) were used as film forming agents.

Glycerol 85% (Bufo) was used as a plasticizer. Disodium edetate (Bufo) was used to bind calcium and magnesium ions that interfere with the cross-linking in carbomer gels. Trometamol (Genfarma) was used to neutralize the carboxylic acid groups of carbomer 974P.

Freshly distilled water was used as a solvent. All other excipients used were of analytical grade.

2.2. Methods

2.2.1. The influence of enalapril on different casting solutions

The solutions pH₁ and pH₂ as listed in Table 1 were used to examine gel formation of HPMC and carbomer 974P at different pH values.

The influence of enalapril on the pH and on the viscosity was tested on the solutions A₀ to A₅₀ and B₀ to B₅₀ (see Fig. 1, series A: HPMC used as viscosity enhancer; series B: carbomer 974P used as viscosity enhancer; the subscript refers to mg enalapril). Note that the concentrations of HPMC and carbomer 974P in casting solutions A and B differ from those in the standard casting solution (SCS, for composition see Table 2). In these experiments an increased amount of film forming agent (compared to SCS) was necessary to measure the viscosity

Table 1

Quantitative composition of the casting solutions used to determine gel formation at different pH and influence of enalapril on the pH and on the viscosity of different casting solutions. Ingredients in grams, water up to 100 g.

Formulation	HPMC	Carbomer 974P	Enalapril	Set pH with trometamol/ HCl
pH ₁	9.48	–	–	To pH 1, 3, 5, 7, 9
pH ₂	–	0.45	–	To pH 1, 3, 5, 7, 9
A ₀	39.24	–	–	–
A ₁₀	39.24	–	0.010	–
A ₂₅	39.24	–	0.025	–
A ₅₀	39.24	–	0.050	–
B ₀	–	1.5	–	–
B ₁₀	–	1.5	0.010	–
B ₂₅	–	1.5	0.025	–
B ₅₀	–	1.5	0.050	–

properly.

Next, the influence of enalapril on the pH of casting solutions A, B and SCS was determined by adding an amount of 10 mg, 25 mg or 50 mg enalapril.

2.2.2. Preparation of the casting solutions and ODFs

The quantitative composition of the casting solutions are listed in Tables 1 and 2. All excipients were dissolved in or mixed with water under constant stirring. After a clear solution had been obtained it was stirred at low speed (100 rpm) with a magnetic bar overnight to allow air bubbles to disappear.

The ODFs were prepared using the solvent casting method as described previously by Visser et al. (2015a). An amount of enalapril (500 mg per 100 g casting solution) was added to the SCS. The abbreviation SCS than changes into SCS_{en} (see Table 2 for composition) to yield ODFs containing 1 mg of this API.

2 mL of the casting solutions (Table 2) were cast onto a release liner (Primeliner® 410/36, Loparex, Apeldoorn, The Netherlands) with a quadruple film applicator using a casting height of 500–2000 µm. The release liner was fixed by vacuum suction to a film applicator (Erichsen, Hemer, Germany). The casting speed was 10 mm/s.

Subsequently, the film layer was dried for 1.5 h at 30 °C and ambient relative humidity (50–60% RH). The ODFs were punched in squares of 1.8 × 1.8 cm using an Artemio perforator (Artemio, Wavre, Belgium). 2 mL of casting solution yielded ten ODFs with size 1.8 × 1.8 cm. All ODFs were sealed in plastic bags and stored in a dark place at room temperature and ambient relative humidity (50–60% RH) before further testing. All tests were performed ultimately within two days after preparation of the ODFs.

SCS_{en} was first used for the preparation of single layer ODFs with different casting heights, 1000 and 2000 µm. The API content of prepared ODFs cast at different casting heights was compared. The API content was determined as described in Section 2.2.4. SCS_{en} was further used for the preparation of an enalapril containing bilayered ODF (see Fig. 2).

2.2.3. Preparation of the bilayered ODFs

The bilayered ODFs were prepared analogously to the double-casting method as described by Preis et al. (2014). For the preparation of a bilayered ODF the first layer of casting solution (as listed in Table 2) was cast using a casting height between 500 and 2000 µm. The film layer was dried for 1.5–8 h (depending on the film forming agent used) at 30 °C and ambient relative humidity (50–60% RH). After drying a second layer was cast. Subsequently, a decision was made which casting height was eligible for further research.

2.2.4. Uniformity of content

Ten ODFs of each formulation were tested for uniformity of content (UoC) for single-dose preparations according to the Ph. Eur. 9th edition,

Fig. 1. Influence of enalapril on the standard casting solution (SCS).

Table 2

Quantitative composition of the casting solutions for examining drug load and development of a bilayered ODF, ingredients in grams. Water up to 100 g.

Excipients	SCS _{en} ^a	SCS ^a	HPC ^a	SA ^a	HEC ^a
HMPG ^a	9.81	9.81	–	–	–
HPC ^a	–	–	10	–	–
SA ^a	–	–	–	8	–
HEC ^a	–	–	–	–	3
Carbomer 974P	0.45	0.45	–	–	–
Trometamol	0.45	0.45	–	–	–
Sodium EDTA	0.045	0.045	–	–	–
Glycerol	1.2	1.2	1.2	2.5	3
Enalapril	0.500	–	–	–	–

^a SCS_{en} = standard casting solution with enalapril yielding 1 mg enalapril per ODF, SCS = standard casting solution, HPC = hydroxypropyl cellulose, SA = sodium alginate, HEC = hydroxyethyl cellulose, HPMC = hypromellose.

method 2.9.6. (European Pharmacopoeia 9th edition). The API content was determined within two days after preparing the ODFs. For each measurement a single ODF containing enalapril was dissolved in 10 mL water and subsequently diluted 20-fold with water. The absorbance of enalapril was measured at 207 nm and corrected for the blank absorbance signal using a UV spectrophotometer Unicam UV 500A (Gemini, Apeldoorn, The Netherlands). A calibration curve of enalapril in water was used to calculate the API content of the ODFs.

2.2.5. Viscosity of the casting solutions

The viscosity of the casting solutions was measured directly after preparation at a temperature of 20 ± 2 °C using a viscometer

(Brookfield, Middleboro, USA). Spindle TA, TB or TC was used for high viscous solutions and spindle 1, 2 or 3 was used for low-viscous solutions.

2.2.6. Thickness

The thickness of the ODFs ($n = 20$) was measured using a micro screw meter (Mitutoyo, Neuss, Germany) at five different points: in the corners and in the middle.

2.2.7. Uniformity of mass

Uniformity of mass (UoM) was determined according to the Ph. Eur. 9th edition: uniformity of mass for single-dose preparations, method 2.9.5, on which also the requirements were based (European Pharmacopoeia 9th edition). Twenty randomly chosen ODFs were weighted individually on an analytical balance. Subsequently the average mass and weight variation were calculated.

2.2.8. Disintegration time

The disintegration time was measured using the method as described recently (Visser et al., 2015a). The ODFs ($n = 5$) were clamped in an arm which moved up and down at a frequency of 30 ± 1 cycles per min, over a distance of 55 ± 2 mm in 700 mL of purified water of 37 °C ± 2 °C. The time at which complete dissolution had occurred was considered as the disintegration time. Analogously to tablet or capsule disintegration, the endpoint was judged by visual inspection. For ODFs the commonly used limit for disintegration time is < 180 s as based on the Ph. Eur. 9th edition, monograph 0478, dispersible tablets (European Pharmacopoeia 9th edition).

Fig. 2. Different pathways for increasing the drug load.

2.2.9. Mechanical properties

The mechanical properties of the ODFs were analysed as described previously (Visser et al., 2015a) using an Instron series 5500 load frames with a load cell of 100 N (Instron, Norwood, USA). The samples were cut using a stamp into a bone shape according to ISO-527 (plastics-determination of tensile properties) (NEN-EN-ISO, 2012). Six samples per ODF formulation were tested. The ODFs were fixed between two clamps that were subsequently moved away from each other with a crosshead speed of 50 mm/min until tearing or breakage of the ODFs. The tensile strength, Young's modulus and elongation at break were recorded. The tensile strength is the maximum force applied to the ODFs until tearing or breakage and was calculated using the following equation (Dixit and Puthli, 2009):

$$\text{Tensile strength} = \frac{\text{load at auto break}}{\times 100 / \text{cross sectional area of the film}}$$

The Young's modulus (which defines the stiffness of the ODFs) and elongation at break were calculated by the computer program from the stress-strain curve.

2.2.10. Mouth feel and stickiness of bilayered ODFs

Five volunteers between 20 and 60 years of age independently evaluated the blank ODFs on mouth feel, namely stickiness to the tongue or palatal. The mouth feel was considered as good if the ODFs stuck to the tongue or palatal immediately. The mouthfeel was considered moderate if the ODFs stuck to the tongue or palatal, but could easily be removed by gentle tongue movements. ODFs that did not stick to the tongue or palatal but floated around in the mouth were

considered as bad.

Based on the results a decision was made which casting height and which combination of layers was eligible for further research.

2.2.11. Scanning electron microscopy

Scanning electron microscopy (SEM) was used to image the bilayered ODFs. The SEM images, with a magnitude of 1000 times, were obtained with a JSM 6301-F microspore (JEOL, Japan) at an acceleration voltage of 10 kV.

3. Results and discussion

From a previous study (Visser et al., 2015a) we learned that some APIs decreased the viscosity of the casting solution and negatively influenced the mechanical properties (strength) of the prepared ODFs upon increasing their load. This effect was particularly striking for enalapril. Enalapril in low doses is used in the treatment of hypertension in paediatrics. Paediatrics is a typical area where ODFs may find a place as extemporaneously prepared dosage forms.

Using SCS good quality ODFs were obtained with 1 mg enalapril. However, a load of 2 mg enalapril led to SCS of which the viscosity was too low for casting (Visser et al., 2015a). Each increment in enalapril load required the addition of extra film forming polymer to the casting solution. This phenomenon is a recognized hurdle in the development of new ODF formulations (Krampe et al., 2016; Visser et al., 2015a).

Below, the results of the influence of enalapril on the casting solution are discussed.

Table 3

Effect of pH change on the viscosity of casting solutions pH₁ and pH₂ (Table 2) judged upon observation.

pH	Casting solution pH ₁	Casting solution pH ₂
1	Milky and liquid	Milky and liquid
3	Clear and viscous	Milky and liquid
5	Clear and viscous	Slightly viscous
7	Clear and viscous	Clear and viscous
9	Clear and viscous	Clear and viscous

3.1. Influence of pH on gel formation

First, gel formation of HPMC and carbomer 974P, the film forming agents used in SCS, was determined at various pH values in the range between 1 and 9. The effect of the pH change on the viscosity and appearance of the casting solutions pH₁ and pH₂ (see Table 1 for composition) was judged upon observation. The results are listed in Table 3.

The viscosity of the casting solution containing HPMC as film forming polymer (pH₁) increased from pH 1 to 3. Upon further pH increase no viscosity change was seen. The viscosity of the casting solution containing carbomer 974P as film forming agent (pH₂) increased more gradually. This is explained by the fact that carbomer has a limited solubility at lower pH values and the anionic polymers in carbomer 974P will expand upon neutralization which results in an increase in viscosity (Bouwman and Bateman, 2015; Kumar and Himmelstein, 1995). Complete neutralization was reached at pH 7. At higher pH no further increase in viscosity was observed.

According to literature carbomer hydrogels need a pH of at least 6.5 for gel formation (Bouwman and Bateman, 2015). We found that gel formation already starts at a pH around 5 but that the maximal viscosity was reached at a higher pH, around 6.5. Upon further increasing the pH no viscosity change was observed.

3.2. Influence of enalapril on gel formation, pH and viscosity

To determine the influence of an increased dose of enalapril on gel formation of casting solution B₀ the pH of the casting solution was set with hydrochloric acid or trometamol at pH 4, pH 5, pH 6 or pH 7.

The casting solutions with a pH of 6 or 7 where so viscous that air bubbles could not be removed and the viscosity could not be measured. These solutions were excluded from further research and the influence of enalapril was therefore only explored on the casting solutions with a pH of 4 and 5. After addition of enalapril the viscosity decreased dose-dependently.

To investigate the effect of enalapril on the pH of casting solutions A, B and SCS, a high dose (see Table 4) of the API enalapril per ODF was added. Enalapril maleate has a pKa of 2.97 (the carboxyl group) and a pKa of 5.35 (the amine group) (PubChem). A pH of 3.09 was found for an enalapril concentration of 1 mg/mL in water. With increasing concentration of enalapril a dose dependent reduction on the pH for casting solutions A, B and SCS was measured (Table 4).

Table 4

Effect of enalapril on pH of the casting solutions A, B and the standard casting solution (SCS).

Enalapril (mg)	pH casting solution A ^a	pH casting solution B ^a	pH SCS
0	7.28	3.20	6.33
10	7.14	3.16	6.28
25	6.68	3.15	6.22
50	5.70	3.04	6.12

^a Casting solution A contains HPMC and casting solution B contains carbomer 974P as viscosity enhancer, the standard casting solution contains HPMC as well as carbomer 974P.

Fig. 3. Influence on viscosity after adding enalapril to casting solution A.

Fig. 4. Influence on viscosity after adding enalapril to casting solution B.

The effect of enalapril was particularly obvious in case HPMC alone was used as the film forming agent. Besides, addition of enalapril reduced the viscosity of casting solution A and to a greater extent of casting solution B (see Figs. 3 and 4).

The influence of additions to HPMC gels on the viscosity has been described in literature. HPMC is non-ionic soluble cellulose ether and ions are known to reduce the viscosity of aqueous cellulose ether solutions by reducing the hydration of the cellulose ethers (Liu et al., 2008; Mitchell et al., 1990; Visser et al., 2015a).

The viscosity of carbomer gels may be influenced by the addition of an API. The API may interact with the cross-linking of the carbomer gels or influence the pH of the casting solution thereby negatively influencing the gel formation. The Newtonian properties of casting solution A and the pseudoplastic behaviour of casting solution B were not influenced by the addition of enalapril.

3.3. Increasing the drug load by increasing the casting height

As first option to increase the enalapril load of an ODF without encountering the problems related to viscosity reduction the casting height was increased. The UV measurements showed that the enalapril content of ODFs cast with a casting height of $1 \times 1000 \mu\text{m}$ was $1.06 \pm 0.01 \text{ mg}$, and the content of ODFs cast with a casting height of $1 \times 2000 \mu\text{m}$ was $1.49 \pm 0.04 \text{ mg}$, using the same enalapril solution. Thus, despite doubling the casting height no doubling of the enalapril content was found. Increasing the casting height does not lead to a linear increase of the drug load when an Erichsen coatmaster 510 is used. According to the manual of the equipment a difference between the wet, cast and dry thickness of a film produced with it has to be taken into account. These differences can be avoided by adding about 30% extra API (Erichsen.de). This implies that for every casting height

applied the amount of API needs to be calculated and adapted accordingly. For each casting height a new casting solution needs to be developed and validated.

3.4. Increasing the drug load by the application of a bilayered ODF

To increase the enalapril load bilayered ODFs were produced using the double-casting method. The API content of a single layer (SCS_{en} , $1 \times 1000 \mu m$) was measured to first confirm the API content of a single layer (see Section 3.3).

Subsequently the bilayered ODF (SCS_{en} , $2 \times 1000 \mu m$) was produced with the double-casting method as described in Section 2.2.3.

The bilayered ODFs were homogeneous, flexible and the layers attached properly. UV measurement showed that the ODFs contained an average of 2.05 ± 0.05 mg enalapril ($n = 12$). This confirms that the drug load can easily be increased by a bilayered ODF.

3.5. Compatibility of film forming agents and characterization of bilayered ODFs

Bilayered ODFs were produced by making combinations of the casting solutions (Table 2) using a casting height of $2 \times 500 \mu m$, $2 \times 1000 \mu m$, $2 \times 1500 \mu m$ and $2 \times 2000 \mu m$. The mouthfeel was evaluated by the small panel of volunteers. The thickness, disintegration time and mechanical properties of the ODFs were measured.

The results are listed in Tables 5 and 6.

The compatibility of different polymers for the production of a bilayered ODF was evaluated.

Preis et al. found that a precondition for double-casting is that the first layer has to be completely dry before casting the second layer. If the first layer was tacky and the second layer was cast on top, a mingling of the layers was observed (Preis et al., 2014). This phenomenon was also seen in our experiments. Thus, complete drying of the first layer is of significant importance.

Preis et al. reported that the ability to form homogeneous bilayers may depend on the polymers used (Preis et al., 2014). We also found that not all combinations of film forming agents were compatible. Besides, the order in which the solutions were cast (as first layer or as second layer) influenced the appearance of the ODFs.

The ODFs prepared with two layers of SCS were homogeneous and flexible. Using casting solutions based on HPC or HEC as the second layer and SCS as first layer, thinner and more flexible ODFs were obtained.

SA as the first layer was not feasible, except when a second layer SA was cast on top of the first SA layer. The SEM image shows no transition between two layers of SA (see Fig. 5). The combination with the other casting solutions yielded ODFs with cracks and the second layer did not attach to the first layer. SA was not feasible as second layer cast on top of SCS either. The SEM image shows that the layers did not attach to each other properly (see Fig. 5). In contrast to our findings Juliano et al. found that SA is applicable as one of the layers in a bilayered film. The

authors developed a bilayered film with the combination SA and HPMC (Juliano et al., 2008). However, no information was provided about the attachment of the layers. Application of two layers of SA yielded ODFs with a very smooth surface, which made it impossible to measure the mechanical properties. The ODFs slipped between the clamps of the Instron apparatus. Besides, the mouthfeel of these ODFs was less favourable in terms of stickiness. The incompatibility of SA with the other layers may be ascribed to the capacity of SA to take up water. This first results in some water uptake from the second layer upon combining the layers and subsequently to evaporation of water. Based on the results obtained, bilayered ODFs with SA were excluded from further research.

HPC as the second layer unexpectedly displayed holes. This might be caused by irregular evaporation of the solvent. The holes may also be caused by a high surface tension of the cast solution. Addition of a surfactant might be necessary to lower the surface tension. However, a further point of attention is that each single excipient may influence the casting solution as well as the stability of the API, which boils down to the conclusion: “less is better”, and would therefore be a reason to reject the use of HPC-based casting solutions.

Another disadvantage of the HPC-based casting solution is the long drying time needed (about 8 h, instead of the usual 1.5 h). Only the ODFs with HPC and without visible imperfections were included for further testing of quality related parameters.

Bilayered ODFs prepared with a casting height of $2 \times 1500 \mu m$ or $2 \times 2000 \mu m$ yielded thick ODFs with unpleasant mouthfeel and were excluded from further research. The remaining and suitable bilayered ODFs prepared with a casting height of $2 \times 500 \mu m$ or $2 \times 1000 \mu m$ were tested on mouthfeel, thickness and mechanical properties and disintegration time. The results are listed in Table 6.

In literature requirements for mechanical properties of only single layer ODFs are described, requirements for bilayered ODFs are lacking so far. According to the Ph. Eur. 9th edition ODFs should ‘possess suitable mechanical strength to resist handling without being damaged’ (European Pharmacopoeia 9th edition). Hoffmann et al. translated these requirements into preferred mechanical properties for single layer ODFs as follows: single layer ODFs should possess a moderate high tensile strength, low Young's modulus and high elongation at break (Hoffmann et al., 2011). In a previous study we defined these requirements for single layer ODFs, cast with the standard casting solution, as a tensile strength of at least $2 N/mm^2$, a Young's modulus of $< 550 N/mm^2$ and an elongation at break of $> 10\%$ (Visser et al., 2015b).

Bilayered films are thicker than single layer films. This will influence the mechanical properties leading to a higher tensile strength. Besides, thicker films are less flexible (Lindert and Breikreutz, 2017). Lindert and Breikreutz also stressed that there are no critical requirements for mechanical properties proposed by the regulatory authorities (Lindert and Breikreutz, 2017). Hence, the requirements as proposed in our previous study (Visser et al., 2015b) may also be applicable for bilayered ODFs taking into account that the use of different polymers will give ODFs displaying different mechanical properties. These requirements may function as a starting point for determining standards for bilayered ODFs.

An important requirement for adequate measuring of the mechanical properties of bilayered ODFs is that the layers attach properly and stay attached during storage. Besides, a strong attachment of the different layers is also a precondition for suitable handling properties, physical stability of the dosage form and patient acceptance.

Most bilayered ODFs (except the combination HPC/HPC) produced with the double-casting method and cast with a casting height of $2 \times 1000 \mu m$ as listed in Table 6 were of good quality and within the proposed limits for mechanical properties. The ODFs cast with a casting height of $2 \times 500 \mu m$ were thinner, displayed a lower tensile strength, a lower elongation at break and the majority displayed a higher Young's modulus. The measured tensile strength was very low in a few combinations of polymers. This implies that these ODFs will break more

Table 5

Compatibility of film forming agents in bilayered ODFs (see Table 2 for composition of the casting solutions).

Second layer →	SCS	HPC	SA	HEC
First layer ↓				
SCS	+	+	–	+
HPC	+	+	+	+
SA	–	–	+	–
HEC	+	+	+	+

SCS = standard casting solution, HPC = hydroxypropyl cellulose, SA = sodium alginate, HEC = hydroxyethyl cellulose.

^a + = compatible; – = not compatible.

Table 6Characterization of bilayered ODFs with a casting height of $2 \times 500 \mu\text{m}$ and $2 \times 1000 \mu\text{m}$, given are means $\pm$ sd.

Combination and casting height	Tensile strength (N/mm ²) (n = 6)	Young's modulus (N/mm ²) (n = 6)	Elongation at break (%) (n = 6)	Thickness (μm) (n = 20)	Mouth feel (stickiness) ^a	Disintegration time (s) (n = 5)
SCS/SCS						
$2 \times 500 \mu\text{m}$	3.8 ± 1.2	505.3 ± 16.9	15.3 ± 5.0	61.7 ± 6.5	+	18.7 ± 1.2
$2 \times 1000 \mu\text{m}$	4.2 ± 0.8	315.2 ± 27.6	25.4 ± 5.5	125.0 ± 8.0	±	79.4 ± 16.8
SCS/HPC						
$2 \times 500 \mu\text{m}$	2.3 ± 0.1	268.0 ± 65.7	14.9 ± 2.8	63.6 ± 9.2	+	19.5 ± 2.1
$2 \times 1000 \mu\text{m}$	2.6 ± 0.2	250.6 ± 25.0	25.3 ± 4.1	129.4 ± 6.6	+	79.3 ± 14.7
SCS/HEC						
$2 \times 500 \mu\text{m}$	2.5 ± 0.3	291.6 ± 63.0	21.5 ± 3.4	47.9 ± 2.6	–	23.9 ± 3.7
$2 \times 1000 \mu\text{m}$	3.1 ± 0.2	344.7 ± 27.8	27.8 ± 3.4	99.0 ± 36.3	–	206.3 ± 32.5
HPC/SCS						
$2 \times 500 \mu\text{m}$	2.9 ± 0.3	321.1 ± 44.7	16.3 ± 2.1	65.2 ± 5.2	+	19.5 ± 2.1
$2 \times 1000 \mu\text{m}$	3.8 ± 0.3	308.2 ± 23.4	27.1 ± 4.0	120.6 ± 13.6	–	79.3 ± 14.7
HPC/HPC						
$2 \times 500 \mu\text{m}$	0.6 ± 0.2	42.2 ± 19.5	59.4 ± 25.5	79.7 ± 13.2	±	17.5 ± 1.6
$2 \times 1000 \mu\text{m}$	1.8 ± 0.2	145.1 ± 12.2	44.8 ± 5.6	117.9 ± 9.7	±	55.4 ± 7.9
HPC/HEC						
$2 \times 500 \mu\text{m}$	1.5 ± 1.0	185.6 ± 41.5	62.5 ± 12.9	64.1 ± 15.0	–	28 ± 2.8
$2 \times 1000 \mu\text{m}$	2.3 ± 0.3	167.0 ± 21.5	70.8 ± 10.1	81.52 ± 15.5	–	83.4 ± 10.3
HEC/SCS						
$2 \times 500 \mu\text{m}$	2.0 ± 0.8	400.3 ± 95.9	25.1 ± 4.6	45.3 ± 11.3	–	23.9 ± 3.7
$2 \times 1000 \mu\text{m}$	3.2 ± 0.5	332.2 ± 43.6	29.2 ± 4.6	98.3 ± 11.8	–	206.3 ± 32.5
HEC/HPC						
$2 \times 500 \mu\text{m}$	1.3 ± 0.1	95.5 ± 15.0	82.6 ± 9.0	44.1 ± 3.3	–	28 ± 2.8
$2 \times 1000 \mu\text{m}$	2.2 ± 0.1	117.9 ± 13.9	103.8 ± 12.5	103.2 ± 5.7	–	83.4 ± 10.3
HEC/HEC						
$2 \times 500 \mu\text{m}$	2.1 ± 1.3	334.8 ± 25.0	108.8 ± 16.2	26.4 ± 4.8	–	20.8 ± 1.4
$2 \times 1000 \mu\text{m}$	3.3 ± 0.7	191.9 ± 25.0	129.6 ± 2806	66.8 ± 13.2	–	72.4 ± 5.3

^a Judgment according to the test panel: + = good; ± = moderate; – = bad.

easily, which is unfavourable in terms of handling properties.

Only a few combinations displayed a moderate to good mouthfeel, namely SCS/SCS, SCS/HPC (or HPC/SCS) and HPC/HPC. The other combinations floated around in the mouth which is unfavourable in terms of patient acceptance. Children might spit out, chew on or even choke on the dosage form.

The combination SCS/HEC (or HEC/SCS) yielded ODFs with a disintegration time longer than 3 min. This is also unfavourable in terms of patient acceptance. The disintegration time should be < 180 s according to the Ph. Eur. 9th edition, monograph 0478, Dispersible tablets (European Pharmacopoeia 9th edition).

All bilayered ODFs tested in this study met the requirement of the Ph. Eur. uniformity of mass with an average mass of 50 mg.

4. Conclusion

The properties of SCS, which contained HPMC and carbomer as film

forming agents, were negatively affected by an increased enalapril load. Enalapril dose-dependently reduced the viscosity of SCS on the one hand by causing a salting-out effect and on the other hand by influencing the pH.

To increase the enalapril load and to circumvent these viscosity problems, the feasibility of a bilayered ODF consisting of two layers SCS was investigated. In conclusion, it is possible to prepare a good quality bilayered ODF consisting of two layers SCS using the double-casting method. This opens perspective for the preparation of ODFs with a higher drug load using the solvent casting method.

Theoretically, for the preparation of a bilayered ODF two layers of different polymers can be used. From our results it became clear that not every combination of polymers leads to an acceptable bilayered ODF. The sequence in which the layers are cast influences the appearance of the bilayered ODFs.

In conclusion, the best formulations can be produced with the polymer combinations SCS/SCS and SCS/HPC. These combinations

Fig. 5. SEM images of a bilayered SA-SA film (left) and SCS-SA film (right).

display good mechanical properties, acceptable mouthfeel and disintegration time.

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