Development of shellac-coated sustained release pellet formulations

Yassin Farag, Claudia S. Leopold*

University of Hamburg, Institute of Pharmacy, Department of Pharmaceutical Technology, Bundesstr. 45, 20146 Hamburg, Germany

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ABSTRACT

Shellac is an important coating material for food products. Since the introduction of aqueous ammoniacal solutions it also regained importance for pharmaceutical applications. Because of the comparatively high dissolution pH of this material, further additives are required if shellac is used as enteric coating material. However, this dissolution behaviour of shellac may be of interest for sustained release or colon targeting applications. In the present study different subcoats containing calcium chloride, citric acid or Eudragit® E, respectively, were applied to immediate release theophylline pellets which were subsequently coated with shellac. Drug release from the resulting pellet formulations was measured. The mechanism of interaction between the modifying subcoat ingredients and the shellac coating was investigated using FT-IR spectroscopy. All formulations with modifying subcoat prolonged drug release. Whereas the effect of calcium chloride was a result of ionic interactions with shellac, the effect of citric acid was a reduction of the degree of dissociation of shellac. The influence of Eudragit® E can be explained by the solubility characteristics of this basic polymer. The application of modifying subcoats is an easy and effective means to achieve sustained release from shellac-coated dosage forms. The choice of a suitable substance and the adjustment of its concentration allow tailor made sustained release profiles.

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1. Introduction

Shellac is the only pharmaceutically used resin of animal origin. It is the purified product of the natural material Lac which is secreted by the small parasitic insect Kerria Lacca on various host trees in South Eastern Asia (Buch et al., 2009; Penning, 1990). It consists mainly of esters of aleuritic acid, butolic acid, jalaric acid and shellolic acid (Cockeram and Levine, 1961; Singh et al., 1974; Wadia et al., 1969).

Shellac has good film forming properties. The films provide high gloss (Trezza and Krochta, 2001) and low permeability for water vapour and gases (Hagenmaier and Shaw, 1991; Luangtana-Anan et al., 2007). Shellac is nontoxic, physiologically harmless and therefore listed as GRAS (Generally Recognized As Safe) by the FDA (Okamoto and Ibanez, 1986). This regulatory status allows the use of shellac as additive in food products where the material already plays a major role as coating for confectionaries and citrus fruits (Hagenmaier, 2002; Mcguire and Hagenmaier, 2001). Since the introduction of ammoniacal aqueous solutions shellac could regain importance for pharmaceutical applications. Shellac coatings can easily be applied from aqueous solutions and they do not show the instability problems of coatings prepared from organic solutions (Limmatvapirat et al., 2007; Specht et al., 1998). Due to its acidic character shellac is mostly used as enteric coating (Chang et al., 1990; Limmatvapirat et al., 2004; Specht et al., 1998).

However, shellac has a comparatively high dissolution pH of about 7.3 (Limmatvapirat et al., 2007) which is unsuitable for the application in conventional enteric coated dosage forms. Because of this high dissolution pH the addition of excipients is necessary to achieve a faster drug release in the small intestine. Nevertheless, it has been suggested previously that this characteristic qualifies shellac for application in colon targeting formulations (Ravi and Kumar, 2008; Roda et al., 2007). The shellac coating layer remains intact during the passage of the stomach until it reaches gut segments with higher pH found in the distal ileum as well as in the transverse and descending colon (Evans et al., 1988; Ibeke et al., 2006). This allows the transport of drugs into the colon for a topical treatment of the colonic diseases. Moreover, the peptidase activity in the colon is lower than in the upper GI tract allowing for the oral delivery of peptide drugs such as insulin (Trenktrog et al., 1996).

Besides colon targeting also sustained release formulations have been developed. Pearnchob et al. investigated drug release from shellac containing matrix tablets. These formulations were prepared either by compression of powder or granules. These tablets provided sustained drug release depending on the drug/shellac ratio (Pearnchob et al., 2002). This concept was further modified by Kanokpongsapiboon et al. by treating shellac containing matrix tablets with additional annealing at different temperatures.
thermal treatment leads to artificial aging, changes in the solubility characteristics of the material and ultimately to a pronounced sustained release behaviour (Kanokpongpaiboon et al., 2005).

The aim of the present study was to offer an alternative to achieve sustained drug release from coated pellet formulations using shellac as the coating material. Since shellac is an acidic material, its dissociation is pH-dependent and the carboxylate groups may interact with cationic structures. These interactions were induced by application of subcoats consisting of citric acid, calcium ions or the cationic polymer Eudragit® E. The subcoat formulations presented in this study should offer different options for the development of shellac coated sustained release drug formulations. Drug release from these formulations was investigated and the mechanism of interaction was analyzed.

2. Materials and methods

2.1. Materials

Shellac (SSB 55 Pharma), Stroeuer Schellack Bremen, Germany; Kollidon® 30 (polyvinylpyrrolidone, PVP), BASF, Ludwigshafen, Germany; Eudragit® E, Evonik Rühm, Darmstadt, Germany; all other chemicals used were of analytical grade.

2.2. Methods

2.2.1. Preparation of coating solutions for subcoat application

Ten different subcoat formulations were prepared. The water soluble polymer polyvinylpyrrolidone (PVP) was chosen to act as a binder and for adjustment of the concentration of the modulating substance in the subcoat. The composition of each formulation is listed in Table 1. The ingredients were dissolved at room temperature under moderate stirring in the respective solvent. The amount of solid was 10% [w/w] for all subcoat formulations.

2.2.2. Preparation of shellac coating solutions

Ground shellac was dissolved in 1.5% [w/v] ammonium bicarbonate solution at 50 °C to a final concentration of 15% [w/w]. As the presence of excess ammonium salt influences the dissolution properties of shellac films, the solutions were heated to 65 °C to remove the excessive ammonium salt in the form free ammonia and carbon dioxide. Evaporated water was replaced. The heating process was repeated until a constant pH was reached. The pH of the final solutions was 7.5 (Mettler Toledo MP 225 pH-meter, Columbus, Ohio, USA).

2.2.3. Coating of theophylline pellets

The subcoat was applied to 50g of immediate release theophylline pellets in a Mini Glatt fluid bed coater (Glatt, Binzen, Germany) with Wurster insert (30 mm diameter, 15 mm gap) using a 0.8 mm two-way nozzle, an atomizing air pressure of 1.5–1.7 bar and a spraying rate of 1 g/min. Final coating levels of the subcoat were 0.5, 1 and 1.5 mg/cm² (Table 1). Inlet air temperature was set to 60 °C for the aqueous coating solutions and 20 °C for the ethanolic solutions. Inlet air pressure was adjusted to 0.3 bar.

The outer shellac coating was applied under the same conditions with 45 g of the subcoat layered pellets. The final shellac coating level was 2.5 mg/cm².

2.2.4. Characterization of coated pellets

After each coating step the pellets were characterized for their coating level, diameter and weight. These values were used as quality control criteria of the coating process as well as the basis for calculation of the required shellac mass for the final shellac coating level.

The average coating level of subcoat and shellac coating was calculated from the difference in theophylline content of coated and uncoated pellets. A sample of 150 mg pellets was dissolved in 250.0 ml of 0.1 M NaOH using an ultrasonic bath. After sufficient dilution with 0.1 M NaOH the theophylline concentration was determined spectrophotometrically at 275 nm using a Lambda 25 spectrophotometer (Perkin Elmer, Beaconsfield, UK).

The weight of a single pellet corresponds to the average weight determined from a sample of 500 pellets. The dimension of the pellets was determined by image analysis using a SteREO Discovery.V8 stereomicroscope equipped with a AxioCam ICC and AxioVision software (all from Zeiss, Jena, Germany). The average radius was determined from at least 500 pellets.

2.2.5. Dissolution of shellac coated theophylline pellets

Dissolution tests were performed at 37 °C with approximately 150 mg pellets in 1000 ml simulated gastric fluid (pH 1.2) and phosphate buffer (pH 6.8; 7.4) using a paddle apparatus at 100 rpm (AT 7, Sotax, Allschwil, Switzerland). Dissolution experiments were run for 2 h at pH 1.2 and 7.4 and for 10 h at pH 6.8. Drug release was recorded spectrophotometrically at 271 nm using a Lambda 25 spectrophotometer equipped with 1 mm flow through Quartz cells.

2.2.6. Preparation of film samples

Film samples for FT-IR investigations were prepared by a casting and evaporation method: Films of shellac in its acid form and Eudragit® E were each prepared from 10% [w/w] ethanolic solutions. The combination of Eudragit® E and shellac in a 1:1 molar ratio was cast onto a glass slide and dried at room temperature.

Table 1: Composition of the coatings of the investigated pellet formulations (CL: coating level, [%]; concentration of the substance [w/w] referred to the total mass of the subcoat).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Composition of the formulation for subcoat application</th>
<th>Kollidon [%]</th>
<th>Solvent [%]</th>
<th>CL [mg/cm²]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>– – – – – – – – – – – – – – – –</td>
<td>10</td>
<td>H₂O</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>– – – – – – – – – – – – – –</td>
<td>9</td>
<td>H₂O</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>Citric acid 1 – – – – – – –</td>
<td>9</td>
<td>H₂O</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>1 – – – – – – – – – – – – –</td>
<td>9</td>
<td>H₂O</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>0.5 – – – – – – – – – – – – –</td>
<td>9.5</td>
<td>H₂O</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>CaCl₂ 1 – – – – – – – – – – – – –</td>
<td>9</td>
<td>H₂O</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>1 – – – – – – – – – – – – –</td>
<td>9</td>
<td>H₂O</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>1 – – – – – – – – – – – – –</td>
<td>9</td>
<td>H₂O</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>1 – – – – – – – – – – – – –</td>
<td>9</td>
<td>H₂O</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>Eudragit® E 1 – – – – – – – –</td>
<td>9</td>
<td>Ethanol</td>
<td>90</td>
</tr>
<tr>
<td>11</td>
<td>1 – – – – – – – – – – – – –</td>
<td>8.5</td>
<td>H₂O</td>
<td>90</td>
</tr>
</tbody>
</table>
ratio referring to their functional groups was dissolved in ethanol to a final concentration of 10% [w/w] solid. The solutions were filtered and cast onto Teflon plates. After evaporation of the solvent at room temperature the films were carefully peeled off and cut into the desired shape.

2.2.7. Preparation of calcium shellac

Calcium shellac was prepared by addition of 1 M calcium chloride solution to the aqueous shellac coating solution. Calcium shellac precipitates from the solution. The addition of calcium chloride was continued until a colorless, translucent solution was obtained. The precipitate was filtered, rinsed with water and dried at 60 °C. Finally, the material was ground in a fly cutter and stored over silica gel until further investigation.

2.2.8. FT-IR spectroscopy

In order to determine possible interactions between the subcoat and the shellac coating FT-IR spectroscopy was performed using a Tensor 37 FT-IR spectrometer (Bruker, Ettlingen, Germany) equipped with a MIRacle™ ATR unit (Pike Technologies, Madison, WI, USA). The respective film or powder samples were fixed to the reflection plate of the ATR unit. The spectrum was calculated from 16 measurements using the OPUS software.

3. Results and discussion

Eleven different shellac coated pellet formulations were prepared and tested for drug release. The formulations contained either no subcoat, a subcoat without modifying substance as blank or a subcoat with different substances at different subcoat coating levels.

The mechanism of drug release at the investigated pH values is shown schematically in Fig. 1. Shellac as acidic material does not dissolve at pH 1.2 maintaining its barrier function and providing gastric resistance. Dissolution testing was also done at pH 6.8, the standard buffer for testing of enteric-coated dosage forms. However, this pH is below the dissolution pH of shellac. At pH 6.8 the material only swells resulting in a reduced barrier function of the coating and allows for water penetration into the pellet core. Drug and subcoat material dissolve and diffuse through the coating layer. The pKₐ of shellac is known to be about 6 (Buch et al., 2009; Farag and Leopold, 2009). Even though the material does not dissolve at pH 6.8, a small amount of its carboxylic groups is dissociated and may interact with the subcoat material. Final dissolution tests were performed at pH 7.4 which is above the dissolution pH of shellac. The shellac coating dissolves followed by liberation of subcoat material and drug release.

Dissolution experiments at pH 1.2 confirmed gastric resistance and film integrity. None of the prepared formulations showed drug release of more than 4% of the dose within 120 min of dissolution testing at pH 1.2. Therefore, all formulations fulfilled the specification of the pharmacopoeias for gastric resistance.

Drug release experiments at pH 6.8 showed a pronounced effect of the subcoat materials on the drug release performance of the investigated pellet formulations. It could be shown, that this effect can be attributed to the embedded substances and not to the presence of a subcoat itself (Fig. 2). In comparison to the formulation without subcoat, drug release from pellets with a blank subcoat (without modulating substance) was altered only negligibly. This slight slowdown in drug release can be explained by the presence of the blank subcoat which represents a diffusion barrier. Other reasons are the time needed for dissolution process of the subcoat material and possibly a competing release of drug and subcoat material. However, all these factors are negligible compared to the release-modifying effect of the modulating substances present in the other subcoat formulations.

In Fig. 2 the effect of the investigated modulating substances on drug release at pH 6.8 is shown. All formulations displayed in this figure have a coating level of the subcoat of 1 mg/cm². This allows a direct comparison of the effect of the modulating substances.

The greatest effect could be shown for the formulation containing citric acid. Citric acid is a tricarboxylic acid with three readily dissociable protons: pKₐ1 = 3.13, pKₐ2 = 4.76 and pKₐ3 = 6.40 (Bates and Pinching, 1949). After placing the pellets in the dissolution medium the shellac coating begins to swell allowing for diffusion of dissolution medium into the pellet core. The dissolution medium dissolves the subcoat material and the embedded citric acid is liberated. At pH 6.8 the citric acid in the subcoat dissociates resulting in a local pH decrease in the pellet core. Since shellac has a high pKₐ, this reduced pH leads to reduced dissociation of shellac, a reduction of film swelling and thus a sustained drug release from the pellet formulation.

This mechanism also explains the sustained drug release observed with shellac coated ascorbic acid pellets ( Förmer et al., 2006). Drug release in that study was performed in water. In addition to the insolubility of shellac in this medium, the ascorbic acid pellet core suppressed a possible swelling of the coating layer. Hence, drug release could only take place through the coating defects mentioned in that publication.

It is well known, that calcium ions interact with many functional groups. This could result in reduced absorption of drugs in the GI tract as e.g. antibiotics (Neuvonen et al., 1991). Also, changes in drug release from drug formulations in the presence of calcium ions have been reported (Baumgartner et al., 2008). Calcium ions accel-
erated drug release from xanthan matrix tablets due to a change in the swelling behaviour of the matrix material. In the present study calcium ions were used to achieve the opposite effect, a sustained release. Shellac forms water insoluble salts with calcium ions. This precipitating effect has been used previously for the preparation of calcium shellac microspheres (Xue and Zhang, 2008, 2009). In the present study the calcium ions were embedded into the subcoat material. After swelling of the shellac coating layer the dissolution medium penetrates into the pellet and dissolves the calcium chloride subcoat. The liberated calcium ions interact with the shellac coating leading to precipitation of calcium shellac. This local precipitation in the coating layer leads to a decrease in film swelling, increased barrier function and thus sustained drug release.

Eudragit® E is a basic copolymer based on dimethylaminomethyl methacrylate, butyl methacrylate, and methyl methacrylate. The polymer is insoluble in saliva but dissolves in the acidic medium of the stomach. Therefore, it is generally used for taste masking applications. Eudragit® E films are insoluble at pH 5 or higher. Below pH 5 the polymer dissolves rapidly by salt formation (Evronik, 2009). In the present study Eudragit® E is combined with PVP in the subcoat. The amount of just 10% Eudragit® E and in the subcoat guarantees that no continuous Eudragit® E film is formed which might inhibit drug release at higher pH.

In comparison to citric acid and calcium chloride the prolonging effect of the Eudragit® E subcoat is found to be less pronounced. In contrast to the other modulating substances Eudragit® E is water insoluble and the pH of the dissolution medium is too high for dissolution of this basic polymer. Thus, no interaction between free base of Eudragit® E and the shellac coating could take place. However, in comparison to the blank subcoat drug release is prolonged. Combined with PVP the insoluble Eudragit® E most likely forms a denser matrix than PVP alone providing a more effective diffusion barrier.

The formation of citric acid to the Eudragit® E-subcoat lowers the pH in the pellet core allowing for protonation of the basic polymer. This addition was intended to clarify whether protonation of the basic polymer led to an interaction with the shellac coat and a possible formation of an interpolymer complex. In fact, dissolution experiments show that a combination of Eudragit® E and citric acid further decreased drug release. However, a comparison with a formulation containing citric acid alone at the same concentration as in the Eudragit® E-citric acid combination subcoat revealed almost identical dissolution profiles. This proved that the decrease in drug release must be attributed mainly to the pH reduction caused by citric acid and not to an interaction of Eudragit® E and the outer shellac coating.

The formation of interpolymer complexes has been well studied for combinations of the basic polymer chitosan and acidic polymers such as sodium carboxymethylcellulose (Gomez-Burgaz et al., 2009), polyacrylic acid (Lee et al., 2008) or Eudragit® L and Eudragit® S (Moustafine et al., 2008). In these studies the interaction of basic and acidic polymer could be identified via FT-IR spectroscopy by the formation of a new band in the area of 1560 cm⁻¹ which could be attributed to the interaction of the carboxylate group of the acidic polymer and the protonated amino group of the glucosamine in chitosan. In Fig. 3 the FT-IR spectra of calcium shellac, shellac acid and Eudragit® E as well as the combinations of shellac and Eudragit® E in a film and in a physical mixture are shown. In the film as well as in the physical mixture characteristic bands of the individual substances can be identified. However, in contrast to the physical mixture a band appears at 1568 cm⁻¹ in the spectrum of the film of the combination shellac and Eudragit® E. This indicates an interaction between the carboxylate group of shellac and the protonated amino group of Eudragit® E. However, this interaction does not seem to significantly affect drug release from the pellet formulations. A possible explanation is the low solubility of both compounds at pH 6.8 although according to their pKₐ values they are both charged to over 90% this pH.

The FT-IR spectra of shellac in its acid form and calcium shellac are shown to clarify the interaction between calcium ions and shellac. Whereas the location and intensity of the C–H stretching vibrations (2925 and 2852 cm⁻¹) remain almost unchanged, distinct changes appear in other areas of the spectrum of calcium shellac. The band in the area between 3700 and 3000 cm⁻¹ is a result of O–H stretching vibrations. This band has a shoulder in the spectrum of the calcium salt and is located next to a small new band at 3031 cm⁻¹. This indicates an interaction of calcium ions with the carboxylate groups as mechanism of salt formation. The intensity of the bands at 1629, 1542 and 1404 cm⁻¹ is significantly increased with calcium shellac compared to its acid form. It has been reported previously that a shift of the carbonyl band (asymmetric C–O stretching vibration) to areas around 1560 cm⁻¹ can be attributed to an interaction between calcium ions and carboxylates (Painter et al., 1982; Pringels et al., 2008). The bands at 1629 and 1404 cm⁻¹ may be referred to the asymmetric and symmetric C–O stretching vibration, respectively, of the carboxylate.
carboxylic groups are involved in this salt formation. 0.5 mg/cm²; of 0.5 mg/cm² already show distinct sustained drug release. After coat was kept constant for these formulations the total amount of shown. As the concentration of modulating substance in the sub- material is deprotonated in the film.

shellac acid spectrum it can be assumed that a small part of the chloride there is no significant difference between the 1 mg/cm² and the 1.5 mg/cm² citric acid subcoat formulations. This can be explained by the mechanism of interaction with the shellac coating. Calcium chloride interacts with shellac by precipitation, citric acid by decreasing the pH and a reduced dissociation of the shellac coating. During the dissolution experiment in addition to the drug material from the subcoat diffuses through the swollen shellac coating layer. This leads to a mass reduction of both materials in the pellet core with on-going dissolution testing. Calcium ions on the one hand interact with dissociated carboxylate groups of shellac. This interaction remains effective as long as sufficient calcium ions are present in the pellet core. Thus, the more calcium ions the denser the shell of precipitated calcium-shellac and the slower drug release. Citric acid on the other hand interacts with shellac coating in a more general way. Here, a reduced dissociation instead of salt formation decreases drug release as long as a low pH is maintained in the pellet core. The presence of dissociated and undissociated acid creates a buffer medium in the pellet core that ensures a constant pH which is almost independent of the citric acid concentration. Hence, above a certain coating level no further change in drug release was observed.

At pH 6.8 the shellac coating layer of all pellet formulations remained intact during the dissolution experiments. This confirms drug diffusion through the intact coating film release mechanism.

In Fig. 5 the drug release profiles at pH 7.4 are displayed for the investigated formulations. At this pH the effect of the subcoats is found to be significantly less pronounced. As pH 7.4 is above the dissolution pH of shellac a different release mechanism is observed. In contrast to pH 6.8 the drug is not released after swelling of the coating layer by slow drug diffusion but by dissolution of the coating layer with subsequent fast drug liberation. Hence, the individual influence of the different modulating substances has changed. The effect of citric acid, which shows the greatest impact on drug release at pH 6.8, is almost negligible at pH 7.4. The dissolution medium rapidly dissolves the shellac coating leading to neutralization of the citric acid in the subcoat. This effect is also observed with the Eudragit® E formulations containing citric acid. The influence of the acid is barely visible in the initial phase of drug release. Once the dissolution medium reaches the pellet core, the acid is neutralized and the release profile approaches that of the Eudragit® E subcoat formulation without acid additive. In comparison to citric acid, the dissolution medium adversely affects drug release from formulations containing Eudragit® E. At pH 7.4 the polymer is insoluble providing a diffusion barrier which prolongs drug release. This effect is also observed for the calcium chloride formulation. The calcium ions interact with the dissociated shellac under formation of insoluble calcium shellac. In contrast to citric acid this precipitating effect of calcium ions is non-reversible under the dissolution testing conditions and leads, as observed with Eudragit® E, to the formation of a diffusion barrier that prolongs drug release. The presence of this barrier could be confirmed by visual examination.
of the pellet samples after dissolution testing. Pellets of formulations with calcium chloride and Eudragit® E subcoats had a jelly-like shell consisting of the respective precipitate.

4. Conclusion

The application of modifying subcoats consisting of citric acid, calcium chloride or Eudragit® E is an effective means to obtain sustained drug release from shellac coated pellets. For subcoats containing calcium chloride and citric acid this prolonging effect can be referred to interactions between the substance and the shellac coating layer. Whereas the effect of calcium chloride is a result of salt formation with shellac the effect of citric acid is a reduction of the degree of dissociation of shellac. In contrast, the influence of Eudragit® E can be explained by the solubility characteristics of this basic polymer. The choice of a suitable substance and the adjustment of its concentration in the subcoat allow tailor made sustained release profiles.

Except for Eudragit® E, all materials used in the investigated pellet formulations are approved for application in food products. Hence, the combination of citric acid or calcium chloride containing subcoats with an outer shellac coating could be of interest for application in sustained release vitamin formulations or dietary supplements.

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References


