Evaluation of critical process parameters for intra-tablet coating uniformity using terahertz pulsed imaging

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A B S T R A C T
The purpose of this study was to evaluate the intra-tablet coating uniformity and the identification of critical process parameters in an active pan coating process using terahertz pulsed imaging (TPI). A design of experiments (DoE) was performed with drum load, drum speed, spray rate, run duration and spray pressure as factors. Different measures of intra-tablet uniformity were investigated: the average thickness on the individual tablet faces, spatial variation in layer thickness over the tablet surface, and the coefficient of variation (CV intra). Data analysis revealed that the process parameters in the investigated parameter space had hardly any influence on the difference in layer thickness of the tablet faces and centre band. No increase or decrease in layer thickness – as described in the literature – was found towards the edges of the tablet face. In overwetted process conditions a higher layer thickness at the centre band edges could be observed. Still, the highest variability in coating thickness was found along the circumference of the centre band rather than the height. In general, higher CV intra of layer thickness were found on the centre bands in comparison with the tablet faces. The analysis of the DoE model revealed that the run duration had the highest influence on the CV intra on the tablet faces. TPI showed high potential in the assessment of intra-tablet uniformity and layer thickness distributions over the whole tablet surface. It was successfully used to identify critical process parameters regarding intra-tablet coating uniformity.

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1. Introduction

In the assessment of film coating quality, the uniformity of the film coating plays an important role. Inter-tablet coating uniformity describes how strongly the layer thickness varies between different tablets in a batch, and a high uniformity is necessary to guarantee consistent functionality in each individual dosage form of the batch. Intra-tablet uniformity describes the variation in layer thickness within an individual tablet, e.g., the differences in layer thickness between the tablet surfaces (faces and centre band) or on a single surface.

High intra-tablet uniformity is especially important in functional film coating, for instance, in prolonged release formulations, where the drug release rate depends on the layer thickness of the film coating. In addition, a poor optical appearance may impact on the patient’s adherence to therapy.

To date, only few studies have investigated the influence of process parameters on intra-tablet coating uniformity. These previous studies employed various techniques including terahertz pulsed imaging (TPI), near-infrared chemical imaging (NIR-Cl), laser-induced breakdown spectroscopy (LIBS), X-ray micro computed tomography (XμCT) and computer simulations. In several of these studies, it was found that layer thickness on the tablet centre bands is lower than on the tablet faces [5,8,15,13,9,3]. One study investigated the influence of the drum rotation speed on the centre band thickness [15], while differences in layer thickness on the two tablet faces were reported in two other studies [5,4].

The distribution of layer thickness on individual tablet faces was the subject of a number of studies [7,10,3,11,9,16]. Contradictory results were reported, either showing an increase [7,10,11] or decrease [3] in layer thickness towards the tablet face edges compared to the centre of the tablet surface. Thus far, the influence of process parameters on the coefficient of variation in layer thickness, as a measure of intra-tablet uniformity, was only investigated by means of computer simulations [3], and systematic experimental data are missing in this context.

TPI is a nondestructive imaging technique that can be used to measure the spatial distribution of layer thickness on pharmaceutical tablets. Due to its relatively high spatial resolution, it shows...
potential as a tool to evaluate intra-tablet coating uniformity. Details on the technique were reported by Zeitler et al. [16] and Shen and Taday [12].

The aim of this study was to use TPI for the quantification of layer thickness uniformity in multiple batches of active-coated tablets. Using a design of experiments (DoE), process parameters were systematically modified, and their influence on intra-tablet coating uniformity was assessed by measuring the differences in layer thickness on the three tablet surfaces (both tablet faces and centre band). Together with the spatial distribution of layer thickness, the coefficient of variation on the tablet surfaces was quantified.

2. Materials and methods

2.1. Materials

Gastrointestinal therapeutic systems (GITS, Bayer Pharma AG, Berlin, Germany) were used as starting material for the subsequent coating process. The GITS consist of a two-layer tablet core with the active pharmaceutical ingredient (API) nifedipine in one part (yellow coloured part of the tablet core) and an osmotic blend in the other part (red coloured). A diffusion membrane is coated on top of the two-layer tablet core, consisting of cellulose acetate and polyethylene glycol. The GITS dimensions were 9.1 mm in diameter and 4.8 mm in height with a mass of 280–283 mg per tablet.

2.2. Pan coating

The aqueous coating suspension consisted of 40% (wt/wt) candesartan cilexetil as API and 60% (wt/wt) polyvinyl alcohol based polymer mixture (Opadry® Colorcon, Dartford, UK) at a total solids content of 29% (wt/wt). Candesartan cilexetil was dispersed in water using a dissolver stirrer (IKA-Werke GmbH & Co. KG, Staufen, Germany); then, the polymer mixture was added, and the suspension was stirred for 45 min.

Pan coating was performed using a side-vented pan coater (BFC50, L.B. Bohle, Ennigerloh, Germany) with a pan diameter of 700 mm and a pan length of 630 mm (cylindrical part of the coating drum). A 2⁻¹ fractional factorial design of experiments was executed with drum load (loa), drum rotation speed (rpm), spray rate (spr), run duration (dur) and spray pressure (pres) as factors. Three replicate runs were prepared at the centre point of the design space. The range of process parameters is detailed in Table 1, and the process parameters for the individual batches are listed in Table 2.

Three of the investigated factors impact on the amount of coating material applied per tablet. The drum load determines the number of tablets in the batch. With a higher drum load, the coating suspension is distributed on more tablets, and the amount of suspension per tablet is reduced when compared to a lower drum load. Both spray rate and run duration were included in the experimental design separately to investigate their effect on coating uniformity. The factor combination of spray rate and run duration determines the total amount of coating suspension applied to the batch. The drum load then determines the amount of coating suspension per tablet. Hence, the amount of coating suspension per tablet varies from batch to batch and is the result of the factor combination of drum load, spray rate and run duration. Depending on the factor combinations in the individual batches, drug loads between 6.6 and 32.0 mg/tablet CAN (covering a therapeutically meaningful CAN dose strength range) were applied (see Table 2). This resulted in an amount of coating mass (i.e. mass increase of the tablets) between 16.5 and 80 mg/tablet.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Abbr.</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>drum load</td>
<td>loa</td>
<td>133–153</td>
</tr>
<tr>
<td>drum speed</td>
<td>rpm</td>
<td>12–14</td>
</tr>
<tr>
<td>spray rate</td>
<td>spr</td>
<td>60–120</td>
</tr>
<tr>
<td>run duration</td>
<td>dur</td>
<td>150–300</td>
</tr>
<tr>
<td>spray pressure</td>
<td>pres</td>
<td>1.7–1.9</td>
</tr>
</tbody>
</table>

Table 1: Range of process parameters in the design of experiments.

Samples were withdrawn from the final product.

2.3. Terahertz pulsed imaging

Terahertz pulsed imaging was performed using a TPI imager 2000 system (TeraView Ltd., Cambridge, UK). The tablets were scanned in full scan mode (both tablet faces and centre band) at a point spacing grid of 200 µm x 200 µm. In total, approximately 1900 and 1700 data points were collected for each tablet face and centre band, respectively. The penetration depth was set to 2 mm in air. Ten tablets per batch were measured, except for batch No. 6, where 11 tablets were measured. A total number of 191 tablets were included in this study.

TPIView software version 3.0.3 (TeraView Ltd., Cambridge, UK) was used for layer thickness analysis. The layer thickness was calculated as $2d_{TH} = \Delta c/n$, where $\Delta$ is the time delay between two subsequent reflection pulses of the incident terahertz pulse, $c$ is the speed of light and $n$ is the refractive index of the coating layer. The refractive index was set to $n = 1.53$, which is the default value and represents the refractive index of a typical pharmaceutical coating polymer [16]. Experimental values of $n$ were not determined for the individual batches, and hence, the layer thickness values in this study are not absolute. In Brock et al. [1], it was shown that $n$ is likely to change between batches with different process conditions. As a consequence of the unknown absolute value of $n$ and the different amounts of coating suspension applied in each batch, the comparison of batches to each other will only be performed using relative numbers. Using X-ray microcomputed tomography as a reference technique to measure the absolute coating thickness, Russe et al. [11] showed excellent agreement of the spatial variation in layer thickness determined by TPI. Hence, it is assumed that the spatial variation in layer thickness over the tablet surface can be accurately described using TPI. As demonstrated previously, optical microscopy is an inadequate reference technique due to the deformation of the film coating during the sample preparation [2] and the fact that only a cross-section with a limited number of measurement points can be used to investigate coating uniformity.

Numerical data analysis was performed using Matlab R2011b (The Mathworks, Natick, USA). Differences in the time-domain signals on the two tablet faces due to the inhomogeneous composition of the bilayered tablet core were reported in Brock et al. [1]. The location of the laser drilled hole, and the fact that the red and yellow part of the tablet core exhibit different time-domain signals, made it possible to assign the coating thickness data to the specific face of the tablet core. According to the colour of the tablet core parts, the yellow part of the GITS is referred to as the ‘yellow tablet face’, while the red part of the GITS is called ‘red tablet face’ in this article. In order to remove artefacts in the TPI measurements close to the tablet edges, a region of interest of 1.5–4 mm radius from tablet face centre was chosen for numerical analysis. For the centre bands, only data points >0.15 mm edge distance were included in the analysis. Further details on measurement artefacts in this specific sample system can be found in Brock et al. [1].
3. Results and discussion

3.1. Face-centre ratio

The average layer thickness on the tablet faces and centre bands was between 90–358 $\mu$m and 76–334 $\mu$m, respectively. In a first step towards analysing the intra-tablet coating uniformity, the variability of layer thickness between tablet faces and centre bands was assessed with respect to its dependence on the selected process parameters.

For this purpose, the ratio of layer thickness on the faces to layer thickness on the centre bands (face-centre ratio, FCR) was calculated as:

$$\text{FCR} = \frac{d_{\text{FP}} (\text{red, yellow})}{d_{\text{TM}} (\text{centre})},$$

where $d_{\text{TM}}$ is the average layer thickness on either red or yellow tablet face and on the centre band of the individual tablet. In total, 20 FCR values were obtained per batch of which 10 related to the red tablet face and 10 to the yellow tablet face.

A high variability of the FCR within the tablets of the individual batches was observed (Fig. 1). The FCR reached values up to 1.33 and in one case a FCR of 0.97 was found, indicating that the layer thickness was lower on the investigated tablet face than on the centre band. The scale of FCR values is in agreement with previously published literature: Ho et al. [5] found that the centre band was up to 33% thinner than the tablet faces, while Malaterre et al. [8] found both significant and insignificant differences in layer thickness on tablet faces and centre bands of oral osmotically driven systems.

The mean FCR varied strongly between different DoE batches, and a DoE model of the average FCR was created to investigate any potentially systematic effects further. Insignificant factors were removed during backward regression until no further improvement of the model could be achieved. The model showed only low goodness of fit and prediction, $R^2_{\text{adj}}$ and $Q^2$ (Fig. 2, left).

The analysis showed that an increase in spray rate from 90 g/min (centre point) to 120 g/min (high level) reduced the FCR by $-0.032$ in the investigated parameter space (Fig. 2, right) leading to a more similar layer thickness on faces and centre band. This might be due to a better spreadability of the coating material at more humid process conditions. However, the coefficient was only $-0.03$, indicating that no major improvements on the average FCR could be achieved. Both run duration and spray pressure did not significantly affect the FCR. The interaction of these two factors only showed a coefficient of $+0.015$ at a $p$-value of 0.043. It is unlikely that the observed significance is of any relevance as on the one hand, the coefficient is very low, and on the other hand, the $p$-value is close to 0.05 in combination with a relatively poor model quality. The drum rotation speed showed no significant influence on the FCR of the round biconvex tablets in this study. The factor was removed during backward regression. This result is similar to a study of Wilson and Crossman [15], who found no significant influence of the drum rotation speed on the layer thickness on the centre band.

In this study, the broadest and narrowest range of values within one batch was from 1.06 to 1.33 and from 1.03 to 1.12, respectively. Further analysis of statistical models revealed that the width of the distribution of FCR values could not be improved considerably either (data not shown).

### Table 2
Process parameters and CAN content in the fixed-dose combination for the investigated batches of active-coated GITS in the design of experiments [1].

<table>
<thead>
<tr>
<th>Batch no.</th>
<th>loa (kg)</th>
<th>rpm (rpm)</th>
<th>spr (g/min)</th>
<th>dur (min)</th>
<th>pres (bar)</th>
<th>CAN load (mg/tablet)</th>
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<tr>
<td>1</td>
<td>38</td>
<td>12</td>
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<td>13.6</td>
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<td>90</td>
<td>255</td>
<td>1.8</td>
<td>15.8</td>
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</table>

Fig. 1. Boxplots of the face-centre ratio for the individual batches. $n = 20$ FCR values per batch. Boxes and whiskers indicate the 10, 25, 50, 75, 90th percentile, $\times =$ minimum and maximum, $\square =$ mean FCR.
3.2. Differences between the two tablet faces

A high disparity was not only found between the mean layer thickness ($d_{m}$) of the centre bands and the tablet faces but also Ho et al. [5] observed differences in layer thickness between the top and bottom tablet faces of up to 10 μm. In order to quantify this property, the ratio of layer thickness between the yellow and red tablet face was calculated as

$$\text{Y : R ratio} = \frac{d_{m} (\text{yellow})}{d_{m} (\text{red})}$$

Values above 1 indicate that the layer thickness is higher on the yellow tablet face and vice versa. Fig. 3 shows the thickness maps of the yellow and red tablet faces of two DoE batches as well as the corresponding Y:R ratio. The coating layer on the yellow tablet face was up to 1.22-fold thicker than on the red tablet face (here: 102 μm on the yellow face and 83 μm on the red face, Fig. 3A, tablet 4).

While the samples in batch three partly showed high differences in coating thickness between both faces, the layer thickness was more uniform in the samples of batch 17. In this batch, the most extreme Y:R ratio was 0.94, indicating that the layer thickness on the red face was slightly higher than on the yellow face. Less variability in the Y:R ratio compared to the FCR was found. The broadest and narrowest range of values was 0.95–1.22 and 0.97–1.08 in batch 3 and 14, respectively.

The fact that a bilayer tablet with different time-domain signals and colours of each layer was used made it possible to link layer thickness values to one specific tablet face. The yellow tablet face exhibited higher thickness values more frequently than the red tablet face (e.g. Fig. 3A). Also, the average layer thickness of the yellow tablet faces was higher than that of the red tablet faces in most batches. However, significant differences in layer thickness on the red and yellow tablet face could only be found in two out of 19 batches. Considerable similarities in the applied process conditions of these two batches could not be observed (batch 4: loa = 43 kg, rpm = 14 rpm, spr = 60 g/min, dur = 150 min, pres = 1.9 bar; batch 19: loa = 40 kg, rpm = 13 rpm, spr = 90 g/min, dur = 225 min, pres = 1.8 bar).

A preferred orientation of the tablet cores in the coating drum, e.g. due to a shift in the centre of mass due to an inhomogeneous distribution of the excipients in the respective layers of the bilayer core, could be a possible reason for these differences.

3.3. Spatial distribution of the film coating

Concerning the spatial distribution of film coating on the individual tablet faces, two contrasting observations are described in the literature. Using computer simulations, Freireich et al. [3] postulate a decrease in layer thickness towards the tablet face edge of round biconvex tablets which is supported by simulations by Suzuki et al. [14] that suggest high shear stresses at the tablet edges. In contrast, Moeltgen et al. [10] and Madamba et al. [7] experimentally found higher layer thickness closer to the tablet edges in their studies using NIR-CI and LIBS, respectively. Russe et al. [11] found uniform layer thickness over the tablet surface in their study using XμCT and TPI. Only at the extreme of the tablet edge (<500 μm), a higher layer thickness was found. This was directly linked to the die geometry, which had a slight discontinuity in its curvature very close to the edge.

In the layer thickness maps in Fig. 3, areas of high and low coating thickness can be identified on the individual tablet faces. The average layer thickness for each radius starting from the centre of the tablet face was calculated from these maps. The radial distribution of coating thickness was calculated (Fig. 4). On the yellow tablet faces, artefacts in the TPI measurements occur in the area of a laser drilled hole (0–1.5 mm, see Brock et al. [1]). Artefacts due to scattering of the THz pulse also appear close to the tablet face edges from 4 mm radius onwards. In this region, strong scattering of the THz pulse leads to TPI waveforms of low intensity and poorly identifiable interface reflection peaks that bias the coating thickness measurements. These areas, that correspond to potentially inaccurate thickness values, are shaded in grey. For further details on measurement artefacts in TPI, the reader is referred to Brock et al. [1].

The results show that layer thickness remained mostly constant over all radii. Only subtle increases or decreases in layer thickness towards the tablet edges were found.

For the centre bands, both distributions in z-direction and in angular direction (i.e. along the circumference) were investigated. Fig. 5 displays the 2D layer thickness maps of two exemplary tablets and the corresponding distributions in angular and z-direction.

The layer thickness varied strongly in angular direction. In most batches, the average layer thickness was constant in z-direction (e.g. Fig. 5, top). The increase in layer thickness at $z = -1.36$ mm in Fig. 5 (top right) is an artefact of the coating thickness measurement due to strong scattering of the THz pulse at the very edge of the centre band.
However, the tablets from two batches (batches 6 and 14) exhibit a higher layer thickness close to the centre band edges (Fig. 5, bottom). In these batches, a slight increase in layer thickness at the tablet face edges was observed as well. The coating processes of both batches have in common that they are characterised by a very high humidity in the tablet bed throughout the coating process leading to local overwetting of the tablets. Such process conditions may facilitate a migration of the film coating towards the tablet edges before the solvent fully evaporates. Even though this finding implies a poorer coating uniformity on the centre band in these batches, the variability in angular direction is still on the same order of magnitude compared to the coating thickness variation in z-direction. Hence, given the poor coating uniformity in angular direction in all batches, the effect of the migration of coating towards the centre band edges does not necessarily dominate the overall coating uniformity of the centre band.

While the data in this study show high variability of layer thickness around the centre band, the simulations by Freireich et al. [3] suggest a uniform layer thickness in the case of round biconvex tablets. The simulations assume that the spray liquid dries immediately when it hits the surface and mass transfer of coating to neighbouring tablets is not taken into account. These assumptions might be the reason why the migration of coating material towards the centre band edges is not observed in the simulation.

### 3.4. Coefficient of variation

The radial distributions of layer thickness presented in Section 3.3 provide information on the variability of layer thickness in a defined direction. As the layer thickness is averaged over radial bins, a variability of layer thickness over the total area of a tablet face (or centre band) cannot be identified anymore. Rather than binning the layer thickness data along the tablet radius, it is also sensible to look at the total variation in layer thickness across the individual tablet surfaces. For this, the coefficient of variation ($CV_{\text{intra}}$) of layer thickness was calculated for each individual tablet face and centre band. An average $CV_{\text{intra}}$ for the tablet faces or centre bands was then calculated for each batch. The values for $CV_{\text{intra}}$ were in a range of 2.7–6.3% and 3.9–10.1% on the tablet faces and centre bands, respectively. Both standard deviation (in μm) and
CV\textsubscript{intra} were higher on the centre bands compared to the tablet faces (Fig. 6).

The higher CV\textsubscript{intra} on the centre band can be explained by the lower amount of coating that is applied to this area. The centre bands are less often exposed to the spray zone, and, during one exposure to the spray coating material is only applied to a part of the centre band rather than the whole centre band area. Due to its relatively flat geometry, it is more likely that coating material is applied to the whole face throughout one spray exposure on the tablet faces.

The CV\textsubscript{intra} from the tablet faces was used to build a DoE model and to identify critical process parameters. A high goodness of fit and prediction was achieved after backward regression (Fig. 7, left). The very high reproducibility at the model’s centre point (reproducibility >0.999) signified a considerably low variation in the replicate experiments (replicate error) in the model. Due to this fact, the model error that describes the imperfections in the model is not on the same order of magnitude as the replicate error, resulting in a poor model validity.

The coefficient plot revealed that a low run duration, low spray rate and high drum load lead to an increase in CV\textsubscript{intra} which means that the coating uniformity on the tablet faces deteriorates (Fig. 7, middle).

Freireich et al. [3] investigated the influence of the spray rate and run duration on the CV\textsubscript{intra}. Their study showed that the CV\textsubscript{intra} decreases with the number of cycles through the spray zone and their simulations predict that an asymptotic value is reached after 100–1000 coating cycles, i.e. a few minutes process time, and hence, the spray rate and run duration did not significantly influence the CV\textsubscript{intra} in their simulations. In contrast, this experimental study revealed that run duration and spray rate had the highest effect on the CV\textsubscript{intra}.

In agreement with Freireich et al. [3], a decrease in CV\textsubscript{intra} with the number of rotations of the coating drum (and hence run duration and coating cycles) was found in this study (Fig. 7, right). We observe an overall trend of decreasing CV\textsubscript{intra} with increasing number of coating cycles, indicating that a more uniform coating can be achieved at longer process times. However, while Freireich et al.
report that an asymptotic value is reached after a few minutes process time the present DoE shows a decrease in CV_{intra} only over several hours (150–300 min process time). In contrast to the study by Freireich et al. [3], the data points in Fig. 7 represent the CV_{intra} of the individual DoE batches at the process endpoint and do not give information on the change in CV_{intra} over process time within a single coating run. Hence, it is not possible to make a statement when an asymptotic value for CV_{intra} is reached.

A higher spray rate improved the CV_{intra}. This might seem counterintuitive as a higher spray rate means that the run duration is shortened given that a constant amount of coating material is applied (less cycles through the spray zone occur for each tablet). On the other hand, the higher spray rate leads to a higher water content of the coating during the coating process which therefore might be able to spread better across the tablet faces. Hence, a more uniform coating can be achieved on the tablet faces.

Freireich et al. [3] revealed that an increase in drum rotation speed leads to a lower CV_{intra} in the case of almond shaped tablets. This can be explained by the fact that a higher drum rotation speed increases the frequency of appearances of the tablets in the spray zone [6], i.e. the number of passes through the spray that each tablet takes per coating run, and as a result a better intra-tablet coating uniformity is achieved. In contrast to Freireich et al. [3], the drum rotation speed did not show a significant effect on the CV_{intra} in our study. It is important to note that the range of drum rotation speeds in this study (12–14 rpm) is much narrower compared to the work by Freireich et al. [3], and different coaters and tablet shapes were investigated in the two respective studies. While a significant effect of the drum rotation speed on the CV_{intra} was not found in the investigated parameter space, it might still be identifiable when the range of drum rotation speed is broadened.

4. Conclusion

In this study, deeper insights into intra-tablet coating uniformity were given, and the dependence on process parameters was investigated.

The face-centre ratio (FCR), as a measure of layer thickness variability between tablet faces and centre bands, was quantified. It showed high variability between the tablets of an individual batch and within multiple batches. Within the investigated parameter space, it was neither possible to improve the span of FCR values nor the average FCR of a batch.

The layer thickness on the yellow and red tablet face was not equal. For some tablets, high differences in layer thickness were found on the red and yellow tablet face. A subtle trend towards higher layer thickness on the yellow tablet faces was observed, but this was only significant in a few batches. Further studies need to be performed to evaluate in how far any density heterogeneities in the composition of the tablet core could be linked to this trend.

For the majority of tablets, we did not observe an increase or decrease of layer thickness towards the tablet face edges as described in other studies. On the centre bands, the highest layer thickness variability was found along the circumference of the centre band. The formation of a thicker coating at the edge of the centre band, as observed at humid process conditions, contributed to layer thickness variability in the same dimensions as the variability along the circumference of the centre band. In addition, higher coefficients of variation (CV_{intra}) were found on the centre bands in comparison with the tablet faces. This was linked to the fact that the centre band is exposed less frequently, and only partially at each pass, to the spray. Run duration, spray rate and drum load were identified as the critical process parameters for the CV_{intra}.

In summary, TPI is a suitable technique to evaluate intra-tablet coating uniformity at a high spatial resolution. It was successfully used to quantify the coating variability and to identify critical process parameters for intra-tablet uniformity.

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References


