European Journal of Pharmaceutics and Biopharmaceutics 139 (2019) 85–92

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Evaluation of the suitability of a fluidized bed process for the coating of drug-eluting stents

Monika Wentzlaff[a,1], Volkmar Senz[b], Anne Seidlitz[a,*]

[a] Institute of Pharmacy, Biopharmaceutics and Pharmaceutical Technology, Center of Drug Absorption and Transport (C_DAT), University of Greifswald, Felix-Hausdorff-Straße 3, 17487 Greifswald, Germany

[b] Institute for Biomedical Engineering, Rostock University Medical Center, Friedrich-Barnewitz-Straße 4, 18119 Rostock, Germany

ARTICLE INFO

Keywords:
Drug-eluting stent
Fluidized bed coating
Model drug content
Coating homogeneity
Coating thickness
In vitro release

ABSTRACT

Drug-eluting stents are often coated using single-stent coating techniques. In pharmaceutical industry, single-tablet coating is unthinkable. Instead large batches of tablets are coated in fluidized bed apparatuses or pan coaters. Therefore, it was the aim of this work to evaluate whether stents can be coated using a fluidized bed process. For this purpose stents were coated with the model fluorescent drug triamterene embedded in ammonium methacrylate copolymer. Different stent lengths as well as different coating yields were assessed and also a drug-free topcoat was evaluated. The coated stents were analysed regarded coating layer mass, drug content, surface structure, coating thickness and drug release. Furthermore, coating yield and stent defect rate were examined. Except for one stent configuration good results were obtained without optimization of process parameters which indicates the suitability of the method to coat large amounts of stents simultaneously in principle. Drug release was tuneable over a wide range of time spans and a wide range of drug loadings was produced. Further work will be necessary to transform the results of this study from a model stent to a clinically relevant product.

1. Introduction

Stents are endovascular prosthesis that are used to stabilize atherosclerotically occluded blood vessels. For this purpose, the stents are crimped onto balloon catheters, advanced to the occluded vessel portion via an access through the femoral or radial artery, and expanded at the site of occlusion. After balloon removal, the stent remains inside the artery to prevent collapse of expanded vessel portion due to elastic recoil. However, even with this mechanical stabilization vessels may be re-occluded due to hyperproliferation and migration of smooth muscle cells. In order to prevent this re-occlusion, stents may be coated with antiproliferative drugs that are released from polymer-based coatings over prolonged periods of times [1,2]. These so-called drug-eluting stents (DES) have however been associated with late and very late thrombosis due to delayed endothelial healing compared to drug-free stents (bare-metal stents, BMS). However, this problem seems to be controllable with new stent designs [3] in combination with strict compliance with the antiplatelet regimen.

Even though the number of approved DES has greatly risen since their first introduction in 2002/2003 in Europe and the US, little detailed information regarding the coating processes is publically available. In general, drug is coated onto the BMS in combination with a polymer using a dip- or spray-coating process. Polymer-free coatings have also been reported [4–6] even in combination with protective topcoatings [7]. Dip-coating is often used in explorative studies, however, more sophisticated dip-coating processes using automated dipping processes in combination with centrifugation to remove excess coating liquid have also been filed as patent [8]. Spray-coating processes often consist of the mounting of the stent onto a rotating mandrel and subsequent spraying of the coating liquid onto the stent [9]. Droplets for spraying may be obtained using two-component atomizing nozzles, ultrasonic or piezoelectric droplet generation [10–12], or electrospraying [13]. Also, approaches containing two or multiple coatings have been suggested [12,14–16]. However, process capability regarding yield, output per time, etc. have rarely been reported.

For pharmaceutical coating of dosage forms, the fluidized bed process is a well established method providing homogenous coating of large batches. Fluidized bed coating has also been considered with respect to stent coating. Schwarz et al. [17] filed a patent in 2000 for fluidized bed coating of stents and mention the high efficiency of the

* Corresponding author.
E-mail address: anne.seidlitz@uni-greifswald.de (A. Seidlitz).
[1] Present address: Glatt Pharmaceutical Services GmbH & Co. KG, Werner-Glatt-Straße 1, 79589 Binzen, Germany.

https://doi.org/10.1016/j.ejpb.2019.03.013
Received 10 January 2019; Accepted 11 March 2019
Available online 13 March 2019

method. Later, a device to protect a stent during fluidized bed coating from mechanical damage was also filed [18] indicating potential problems associated with the mechanical stress acting on the stent body during fluidized bed coating. Niu et al. [19] also report on the coating of stents in a fluidized bed, however, in this study only 4 stents were coated. It was the aim of this study to examine the applicability of a standard fluidized bed apparatus (small scale in consideration of pharmaceutical processes) for the coating of a large quantity of stents and to examine the stents produced via this method. Since the drugs typically coated onto stents are high potential drugs, which require total containment, the model drug triamterene was used for this study. The substance was chosen because of its good detectability via fluorescence spectrometry and poor water solubility (28 µg/mL [20]) which is also typical for drugs delivered via stents (Paclitaxel 1 µg/mL [21], Sirolimus 2.6 µg/mL [22]). Because of the experiences with pharmaceutical polymers, ammonium methacrylate copolymer was chosen as a model polymer. A lab scale table top fluidized bed apparatus was employed for the coating procedure and the coated stents were examined regarding model drug content, coating morphology and in vitro model drug release.

2. Materials and methods

2.1. Materials

Stent bodies were generously supplied by Cortronik GmbH (Germany). Polymethacrylate dispersion (Eudragit® RS 30D) was kindly donated by Evonik Industries AG (Germany). Steel springs were purchased from Gutekunst & Co KG (Germany). Triamterene was obtained from Sigma Aldrich Chemie GmbH (Germany), formic acid, sodium chloride and disodium hydrogen phosphate from AppliChem GmbH (Germany), triethyl citrate from Alfa Aesar GmbH & Co KG (Germany), potassium dihydrogen phosphate from Neolab Migge (Germany). All further materials were of analytical grade.

2.2. Stent coating

All coating procedures were conducted using a Mini-Glatt® fluidized bed apparatus equipped with the Mikro-Kit® product container (Glatt GmbH, Germany). In order to optimize the fluidization behaviour for stent coating, the process filters were exchanged for a planar filter gaze that was inserted at the outlet of the product container. Furthermore, a custom-made partially conical bottom plate with a mainly central air steam was designed in order to improve fluidization of the stents. This bottom plate is depicted in Fig. 1.

Spraying was performed in bottom spray modus using a spray nozzle with a diameter of 0.3 mm (Düsen-Schlick GmbH, Germany). The spraying liquid was inserted using a roller pump (Ismatec MCP, IDEX-Health & Science GmbH, Germany) equipped with silicone tubing with a diameter of 2 mm. The used process parameters, which had been identified as in preliminary studies, are listed in table 1. The process was driven with conditioned pressurized air (dew point −45 °C). A heating phase of 5 min prior to spraying and a drying time of at least 2 min after the end of spraying were included in the process.

Stents were coated with the fluorescent model substance triamterene suspended in a dispersion of ammonium methacrylate copolymer (Eudragit® RS 30 D). This model drug was chosen due to its low solubility in water which is also typical for drugs used on stents. The use of a clinically relevant drug was not possible since the fluidized bed apparatus available offered no containment system. Further components of the spray liquid were formic acid, triethylcitrate and purified water. The exact composition of the coating liquid is given in table 2. The coating liquid was prepared by dissolving triamterene in formic acid. Under stirring, purified water with dissolved triethylcitrate was added resulting in precipitation of the model drug thus forming a milky suspension. The polymer dispersion was carefully added to this suspension under gentle stirring. The dispersion was continuously gently stirred during the experiment.

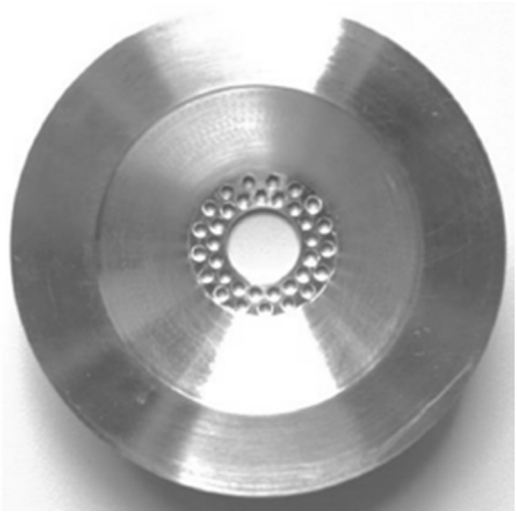

Fig. 1. Custom-built bottom plate for stent fluidization.

Table 1
Selected process parameters for coating.

Parameter	Selected value
Process pressure	0.15 bar
Inlet air temperature	40 °C
Spraying pressure	0.5 bar
Spraying rate	approx. 1.5 g/min

Table 2
Composition of the coating liquid.

Substance	Function	Amount (%)
Ammonium methacrylate copolymer dispersion	Polymer	3.21
Triamterene	Model drug	0.24
Triethylcitrate	Plasticizer	0.19
Formic acid	Pre-solvent for model drug	8.04
Purified water	Dispersion agent	88.82

Using the same process parameters as given in table 1, 9 batches of 50 stents each (length 15 mm, unexpanded diameter 1.6 mm) were coated under addition of 625 steel springs per batch of similar measures (length 14.6 mm, diameter 1.76 mm). The springs were added to achieve a suitable filling level of the product container. This resulted in a theoretical total surface area of the coating goods of 36578 mm^2. An image of the used type of stent and steel spring is given in Fig. 2. The coating time and used masses of spraying liquid were varied to achieve 3 different coating masses (low, intermediate, and high coating mass with theoretical model substance deposition of 2.5, 5 or 12.5 µg/mm^2 surface area) with 3 batches per mass.

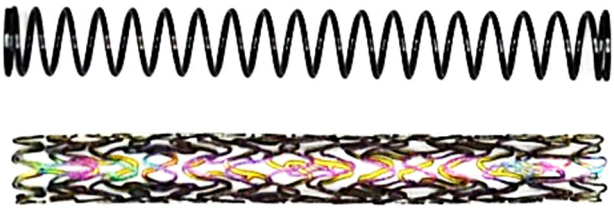

Fig. 2. Images of the type of steel spring (top) and stent (bottom) used for fluidized bed coating.

Table 3
Overview of the different coating approaches, TC = topcoat.

Name	Stent length (mm)	Theoretical model substance load (μg/mm^2)	Number of batches	Amount of spraying liquid used (g)
15mm_2.5 μg/mm^2	15	2.5	3	36.34
15mm_5.0 μg/mm^2	15	5.0	3	73.67
15mm_12.5 μg/mm^2	15	12.5	3	186.80
09mm_12.5 μg/mm^2	9	12.5	3	186.80
30mm_12.5 μg/mm^2	30	12.5	3	186.80
15mm_2.5 μg/mm^2_TC	15	2.5	1	36.34 + 33.25 TC

In addition, 6 batches of 50 stents each of different length (9 mm or 30 mm, respectively, unexpanded diameter 1.6 mm) were coated with the same process parameters and theoretical model substance deposition of 12.5 μg/mm^2 surface area (also used for high coating mass with the 15 mm stents). In order to obtain a comparable total surface area of coating goods the number of steel springs was adjusted accordingly (651 springs added to 50 stents of 9 mm length and 564 springs added to 50 stents of 30 mm length, respectively). However, the same type of spring (length 14.6 mm, diameter 1.76 mm) was used in spite of the changes of stent measures.

In addition, 1 batch of 50 stents (length 15 mm, unexpanded diameter 1.6 mm) and 625 steel springs was once again coated with the low coating mass of 2.5 μg/mm^2 surface area and then coated with the same polymer dispersion without the model drug and formic acid to form a drug-free topcoat containing the same amount of polymer as the drug-containing coat.

An overview of the different coating approaches is given in table 3. The names for the coatings are composed of the stent length in mm and the theoretical model substance load per surface area in μg/mm^2.

The yields of the coating process were analysed in terms of the coating deposition rate and the stent defect rate. The mass of each batch of stents and coated steel springs was determined prior to and after coating and removal of loose material, if applicable, by weighing. The mass gain during coating was divided by the mass of the solid contents of the spraying liquid to determine the deposition rate of the coating liquid in per cent. The stent defect rate was determined by microscopic examination of the stent bodies of all stents (50 stents per batch, Axiovert 200 with Axiovision software, Carl-Zeiss MicroImaging GmbH, Germany). A stent was considered defect when at least one ending was deformed to a diameter of less than 1 mm which would complicate stent mounting on a balloon catheter or when the stent was bent at an angle of more than 10° from to the originally straight shape. The stent defect rate is given in per cent of the total number of stents coated per batch.

2.3. Examination of coated stents

The coating layer mass per stent was determined by individually weighing 10 stents per batch after coating using a suitable scale (Sartorius SE 2, Sartorius AG, Germany). After complete removal of the coating including model drug with acetone and subsequent drying the mass of the same stents was again individually determined. The difference between the two mass determinations is given as the coating layer mass, means and standard deviations (SD) of n = 10 are reported for each batch.

The model drug content per stent was determined by eluting the model drug from the coating. For this purpose 10 stents per batch were individually incubated in 10 mL methanol. The stents were periodically removed from the medium and placed in fresh methanol. The methanol volume employed for elution was reduced as drug content declined. This procedure was repeated until no further elution was detected. Methanolic samples were diluted with the same volume of phosphate buffered saline solution pH 7.4 according to Ph. Eur.. Two samples of each probe were transferred to a 96-well-plate and fluorescence intensity was determined against a calibration series in the same media using a fluorescence reader (Varioskan Flash, Thermo Scientific, USA, excitation wave length 370 nm, emission wave length 434 nm). Based on this, individual drug loads were determined and means and standard deviations of n = 10 per batch are reported.

The appearance of the coating was examined via microscopy. For this purpose, fluorescence microscopy (Biozero-8000, Keyence Corporation, Japan, filter GFP-BP, excitation wave length 360 nm, emission wave length 460 nm) and scanning electron microscopy (Phenom, FEI-Company, USA) of randomly selected stents was performed. Scanning electron microscopy (SEM) was conducted after drying of the stents, cleaning with pressurized gas and sputtering (mini-sputter-coater SC7620, Quorum Technologies, UK, gold/palladium with argon). Selected stents were also examined after balloon expansion to a nominal diameter of 3.5 mm using a Pantera catheter (pressure 6–7 bar for a duration of 10–15 s).

In order to determine the coating thickness randomly selected stents were embedded in epoxy resins (EpoThin, Buehler, Germany) and grinded and polished to obtain longitudinal microsections of the stent. Using these samples, analysis of coating thickness on the abluminal and luminal side of all cut struts along the longitudinal section was performed by analysis of microscopic images (Olympus LEXT OLS 3000, Olympus, Japan) of the individual coated struts which were aligned in two rows. All fully cut struts were considered with five measurement points on the luminal as well as abluminal side of each strut. Two or three stents from one batch were examined per coating approach. Means and standard deviations from these measurements are reported.

Model drug release was examined using an incubation setup. Stents were expanded by means of a balloon catheter as described above and placed in upright standing vials with 10 mL of phosphate buffered saline solution pH 7.4 according to Ph. Eur. preheated to 37 °C. The vials containing the stents were placed on an incubation shaker (Inkubator 1000 with Titramax 1000, Heidolph Instruments, Germany) at 37 °C and 300 revolutions per minute. Media was completely replenished at predetermined time points. The time points for media change were chosen to assure sink conditions during the entire experiment. After stent removal media samples were transferred to a 96-well plate and fluorescence intensity was determined as described above. Model drug release is presented as total cumulative released mass of model drug per stent and means and standard deviations of n = 4 per batch are given.

3. Results and discussion

3.1. Coating process

Stent fluidization was possible using the chosen apparatus and process parameters. In order to obtain a stable fluidization with the slotted objects a comparably high inlet air pressure was necessary which also caused a wide expansion of the fluidized bed. In order to avoid contact with the filter dome, the filters were removed and replaced by planar filter gaze. Optimization of the fluidization process was obtained using the custom-made bottom plate. This bottom plate allowed for a central upwards movement which reduced the wall contact compared to a upwards movement over the entire bottom surface while the conical form of the outer rim assured that deposited stents slid towards the central fluidization air.

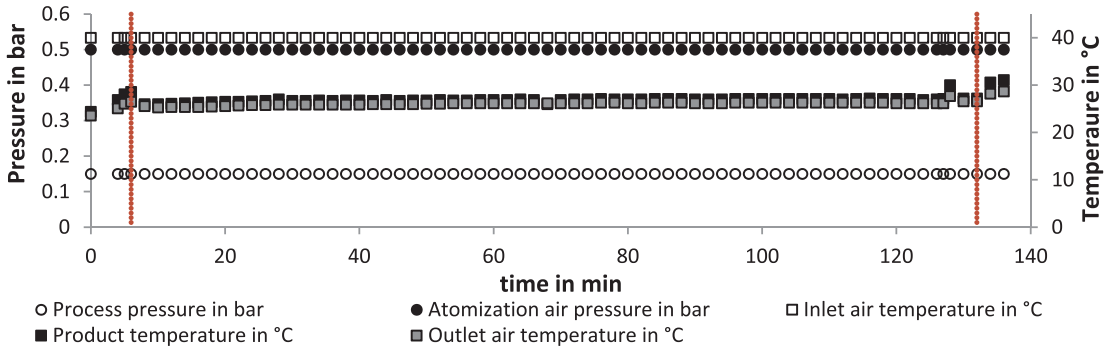

Fig. 3. Representative process data recordings for one batch of stents coated with the high coating mass (15mm_12.5 µg/mm^2), red lines marking the beginning and ending of spraying.

All coating processes were successfully completed with the intended process parameters. In Fig. 3 representative process data recordings for one batch (15mm_12.5 µg/mm^2) are shown.

It is evident that the process parameters only underwent slight changes over time and nearly the same conditions were achieved throughout the entire experiment. Almost identical profiles, even though with different processing times, were achieved for the other batches using the same process parameters. This approach was chosen in order to exclude the influence of these parameters on the outcome. In an alternate experiment using the same stent and coating liquid, changing the spraying pressure from 0.5 bar to 1.0 bar (and, as a consequence of this, increasing in the process air pressure to 0.3 bar) led to a different distribution of the abluminal and luminal coating and to thinner coatings in general and also led to an increase in the defect rate (data not shown). In order to exclude such influences, the same processing parameters were chosen for all batches presented here. Further optimization of coating processes and the resulting attributes, such as yield and defect rate, may however be achieved when adapting these parameters for individual coating approaches and individual batches. Also, it must be kept in mind, that the main portion of coating goods in the experiments presented here were the same type of steel springs independent of the used stent length. It must be expected that a batch consisting exclusively of stents might show a different fluidizations behaviour and fine tuning of the process parameters will be necessary. Because of the limited availability of uncoated stents, however, the approach of adding springs as dummies was the only possibility to conduct these experiments with a suitable filling of the product container while using fresh stents for each experiment. If the stents not chosen for examination had been re-used for the next experiment, the mechanical stress acting on the back bone might have been expected to increase and results regarding the defect rate would not have been reliable. Unfortunately, the springs were not available in measures resembling the 9 mm and 30 mm stents. Alternate dummies, e.g. unslotted cylinders composed of wood, pieces of tubing or wire-end ferrules, which were all tested prior to using steel springs, did not show the same fluidization behaviour and in some cases separation of the fluidized bed was observed. Therefore, the springs were the best available choice to achieve suitable filling. However, separation of the fluidized objects cannot be completely ruled out, even though such processes were not visually observed.

Process spraying times (excluding 5 min of preheating and 2 min of drying), process yields and defect rate are given in table 4. Process times ranged from 22 min of spraying time to 130 min for one batch. During this time, 50 stents were coated. However, simultaneously 625 steel springs were also coated, which were merely added to the process in order to provide sufficient filling of the fluidized bed coater, as described above. In order to keep the total surface area of coating goods constant, slightly different amounts of springs were coated along with the 9 mm stents (651 springs) and the 30 mm stents (564 springs). Therefore, coating of more than 600 units in the given process time was possible and the number of coated units could possibly be further increased when using the coater without the miniaturization set of even a larger fluidized bed apparatus. To date, single unit coating techniques have been described for stent coating. Such techniques have been reported to yield 5–10 coated stents per hour [23,24]. These numbers are in great favor for the fluidized bed coating process, if the defect rate obtained using this method is acceptable. The obtained process yields using this technique were all > 40% which means that the mass increase of the total batch mass after coating was 40% of the totally sprayed solid content. Compared to pharmaceutical scale coating, e.g. of solid oral dosage forms, this is a poor outcome which might be somewhat improved by optimizing the filling of the product container. Nevertheless, it will remain more challenging to obtain a very high yield when spraying at slotted hollow objects which furthermore expand widely during fluidization compared to solids. For single stent coatings hardly any data is available, but yields < 5% have been reported [23]. This number also shows the great efficiency that may be achieved using the fluidized bed process. The obtained defect rate was also very acceptable when considering the immense mechanical stress acting on the dosage form in fluidized bed coating compared to single stent coating. Typically, defect rates between 1% and 8% were obtained. A tendency of higher defect rates with longer coating times was observed. The only process leading to a devastating defect rate under the chosen conditions was the coating of the 9 mm stents of which 73% of the coated stents showed defects. In these experiments the main observed defect was the deformation of the stents endings to diameters below 1 mm. Most likely, the fluidization behavior of these stents deviated most from the added stainless steel springs resulting in a stronger mechanical stress acting on the stent platform associated with more frequent or more intense collisions either with the walls of the container, the steel springs or other stents. Possibly, this problem may be overcome by adjusting the length of the added dummies and the process pressure.

3.2. Examination of coated stents

The mean coating layer masses and model drug loads per stent of each coating approach are given in table 4. In addition, the individual mean results of each batch for these parameters are depicted in Fig. 4. In general, an acceptable reproducibility between batches of the same coating approach was obtained. The largest relative standard deviation regarding model drug content in one batch (standard deviation in percentage of drug content) was observed in batch 3 of the 09mm_12.5 µg/mm^2 stents amounting to a drug load of 217 ± 31 µg. For the other two batches of these stents mean values of 221 µg and 201 µg and standard deviations of 14 µg and 8 µg were detected.

In literature, little information regarding the variation of drug loads of stents is reported. Petersen et al. [16] have described coating layer masses of 240 ± 20 µg as well as 460 ± 20 µg for a coating process providing a two step coating approach with specific luminal or

Table 4
Results of the examination of process yield (means of n = 3 processes ± SD except to topcoat n = 1 batch), defect rate (means of n = 3 batches ± SD except for topcoat n = 1 batch, all stents evaluated) coating layer mass (means of n = 30 stents (10 stents per batch) ± SD except for topcoat n = 10 stents), model drug content (means of n = 30 stents (10 stents per batch) ± SD except for topcoat n = 10 stents) and luminal and abluminal coating thickness (means of n = 1–3 stents with ≥ 20 measured struts per stent ± SD from one selected batch of each coating approach) of the coated stents.

Name	Approx. process spraying time (min)	Process yield (%)	Defect rate (%)	Coating layer mass per stent (µg)	Model drug content per stent (µg)	Coating thickness luminal (µm)	Coating thickness abluminal (µm)
15mm_2.5 µg/mm^2	22	47 ± 1	1 ± 1	355 ± 16	62 ± 5	5.0 ± 2.9	8.8 ± 3.9
15mm_5.0 µg/mm^2	54	41 ± 3	2 ± 0	675 ± 14	110 ± 12	9.0 ± 4.0	13.3 ± 3.8
15mm_12.5 µg/mm^2	130	42 ± 3	8 ± 0	1740 ± 85	271 ± 15	19.4 ± 6.5	28.4 ± 6.5
09mm_12.5 µg/mm^2	130	45 ± 1	73 ± 13	1086 ± 46	213 ± 22	30.8 ± 5.7	25.6 ± 5.8
30mm_12.5 µg/mm^2	130	43 ± 2	6 ± 0	3468 ± 175	690 ± 75	20.3 ± 5.1	24.2 ± 2.9
15mm_2.5 µg/mm^2_TC	20 + 22 TC	45	0	592 ± 23	65 ± 4	14.0 ± 3.7	19.0 ± 2.7

abluminal location of the coating. These deviations are in the same order of magnitude as the deviations observed here. Also, drug content analysis of the previously marketed Cyper Select® + stent yielded mean drug contents of 172 ± 18 µg (n = 5) [25] which is also similar to the results obtained using the fluidized bed process.

Images of coated stent portions obtained with the fluorescence microscope and of single struts obtained in scanning electron microscope are given in Fig. 5. In general, smooth and form fitting coatings were produced. Small defects and surface roughness were observed, especially with increasing process times. This may be explained by a higher amount of mechanical stress acting on the stent body as well as the coatings. This may result in abrasion, spalling and peeling of previously coated material and the resulting loose material as well as polymer sprayed onto the container walls etc. may be re-integrated into the coating resulting in uneven surfaces. It is often assumed that stent surfaces need to be smooth. However, to the authors knowledge there is no clinical proof of this concept. Dibra et al. [26] performed a study with electropolished vs. sandblasted uncoated stents and evaluated late lumen loss as primary study endpoint. No definite superiority of one surface topography was statistically shown but a tendency was observed that a better outcome was obtained with the rough surface. Large delaminations, webbings or polymer bridges were not observed for the stents coated with the fluidized bed process. Even upon stent expansion to a diameter of 3 mm with a catheter pump (data not shown) only very few coating defects in the zones of deformation were observed. Coating split-off or delaminations were not observed during these experiments. Commercially available stents have also been shown to possess small defects before and after expansion, as for example illustrated by Basalus et al. [27].

Coating thicknesses on the luminal and abluminal side of the fluidized bed coated stents are listed in table 4 and representative images of resin embedded strut cross-sections are given in Fig. 5. In general, a thicker coating was present on the abluminal side with a ratio of abluminal/luminal coating of 1.2 to 1.8. Such a tendency towards thicker

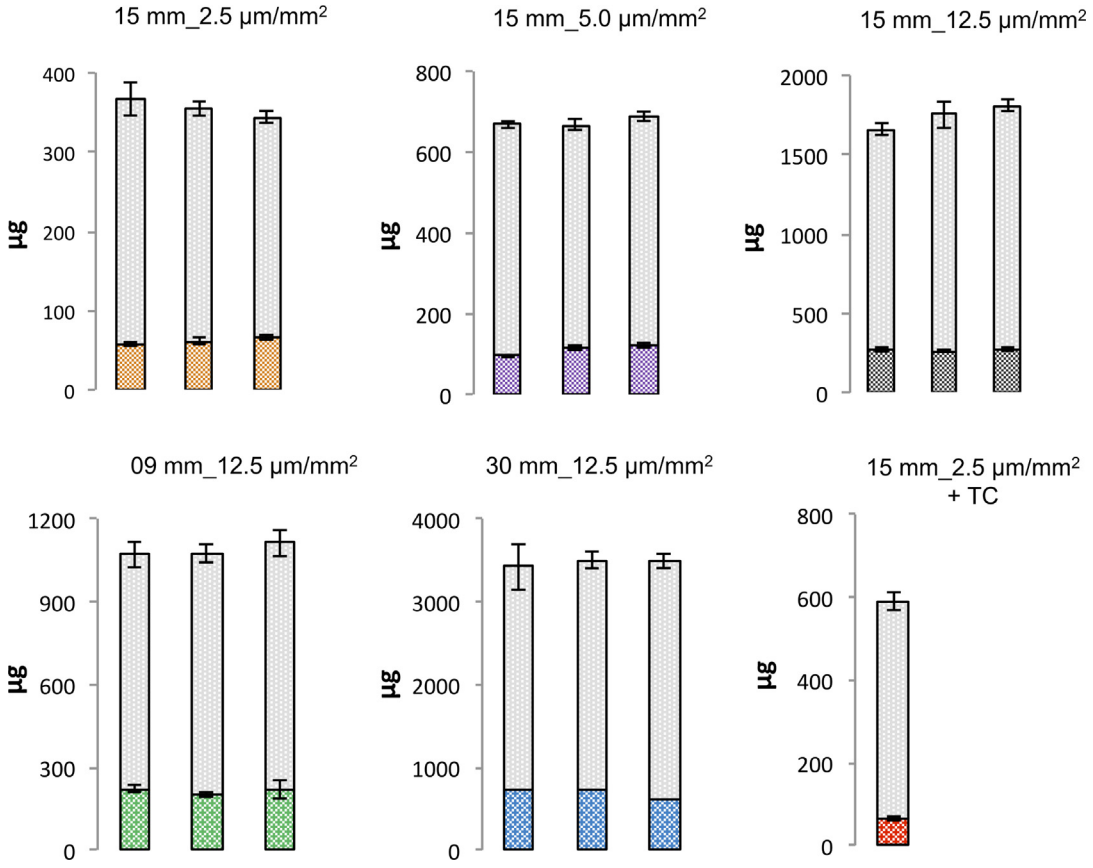

Fig. 4. Model drug loads (colored portion of bar) and coating layer masses (entire bar) of the individual batches obtained with the different coating approaches as indicated, n = 10 per batch, means ± SD.

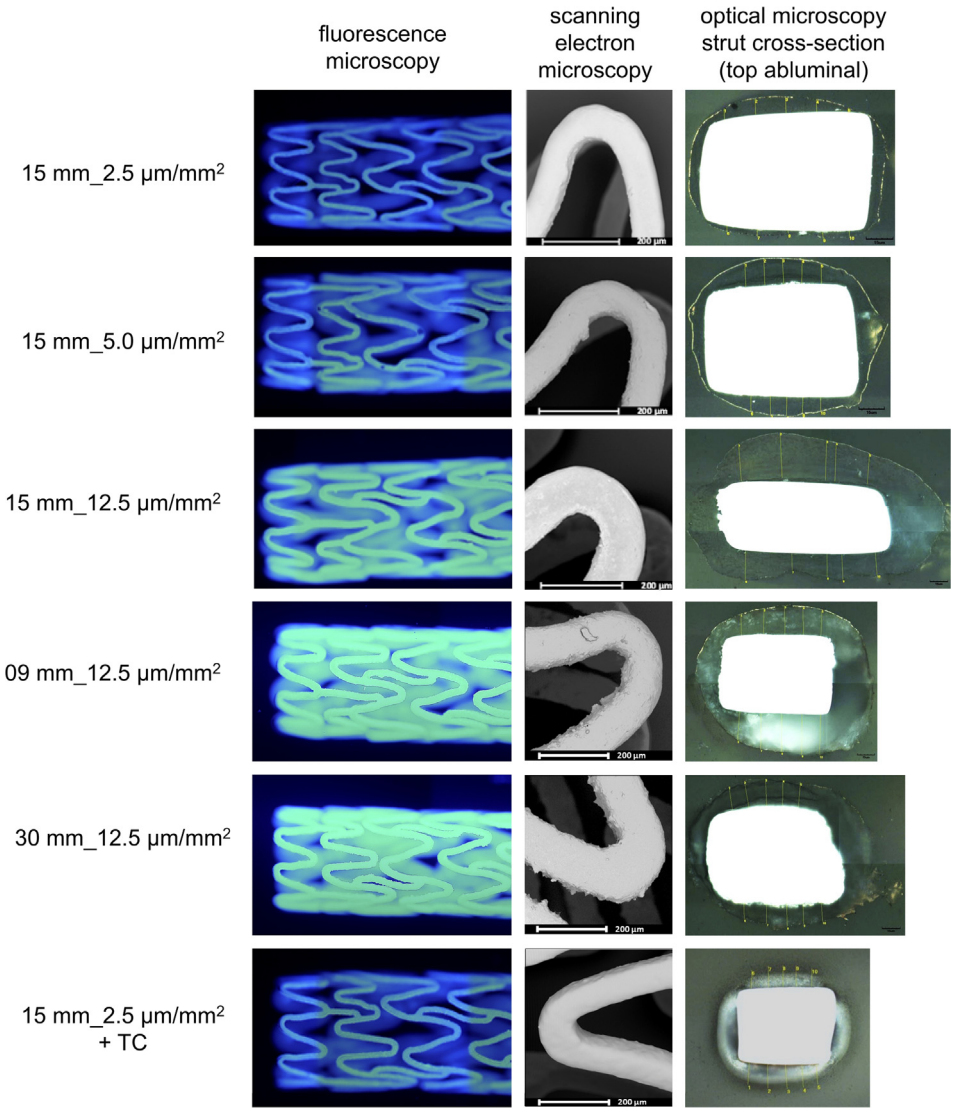

Fig. 5. Images of coated stent portions obtained with the fluorescence microscope (first column), of single struts obtained in scanning electron microscope (middle column, top view) and of resin embedded stents struts (last column, cross-sections of metal strut in white surrounded by the coating) for the different coating approaches as indicated, bars indicating 200 µm in the scanning electron microscopic images and 15 µm in the cross-seticon images.

abluminal coating has previously been observed for spray-coated as well as dip-coated stents [28–31]. The exception from this tendency to thicker abluminal coatings in this set of experiments is the 9mm_12.5 µg/mm^2 coating in which a thicker luminal coating was observed. The reason for this is unclear. The high defect rate indicating high mechanical stress may implicate that this increased stress also caused increased wear of the coating during the process. However, the yield of coating liquid was comparable to the other processes. The thinnest coatings were observed at the corners of the struts, a tendency which is likely to influence drug release in combination with the asymmetric coating distribution as previously discussed [29].

Mean release profiles of one selected batch of each coating approach are depicted in Fig. 6. For better comparison, release profiles of the high mass coating (length 15 mm) is also shown in Fig. 6b whereas the profile from the low mass coating (length 15 mm) is repictured in Fig. 6c. In general, very similar releases were observed in the individual batches. Releases of up to 200 days were observed for the high mass coating (15 mm_12.5 µg/mm^2). For the low coating mass (15 mm_2.5 µg/mm^2) release was nearly finished after 21 d whereas the intermediate mass coating (15 mm_5.0 µg/mm^2) released the model drug for approximately 50 d. The release studies of the other coating approaches were discontinued after approximately 40 days even though a release was not completed at this time. In case of the coating with the drug-free topcoat, only approximately 21 ± 1% of the total drug load had been released during the time span of 39 d. The 9 mm_12.5 µg/mm^2 stents had released 62 ± 3% in 36 d and the 30 mm_12.5 µg/mm^2 stents had released 54 ± 2% during 39 d. At approximately the same time, the 15 mm_12.5 µg/mm^2 stents had released 61 ± 1%. Since no lag phase was observed and the topcoat was directly added after the drug coating using the same polymer and solvent, it must be assumed, that the topcoat contains portions of the drug that were transferred to the “drug-free” layer by dissolution of previously deposited drug.

4. Conclusion

Stents were successfully fluidized and coated using a standard fluidized bed apparatus with a custom-built bottom plate. Even though the process parameters were not optimized for the different coating masses and stent configurations, all batches were coated with good reproducibility. All batches, except for the ones with the shortest stents (9mm_12.5 µg/mm^2) showed comparable good coating liquid yields and acceptable defect rates while providing a very fast coating of a

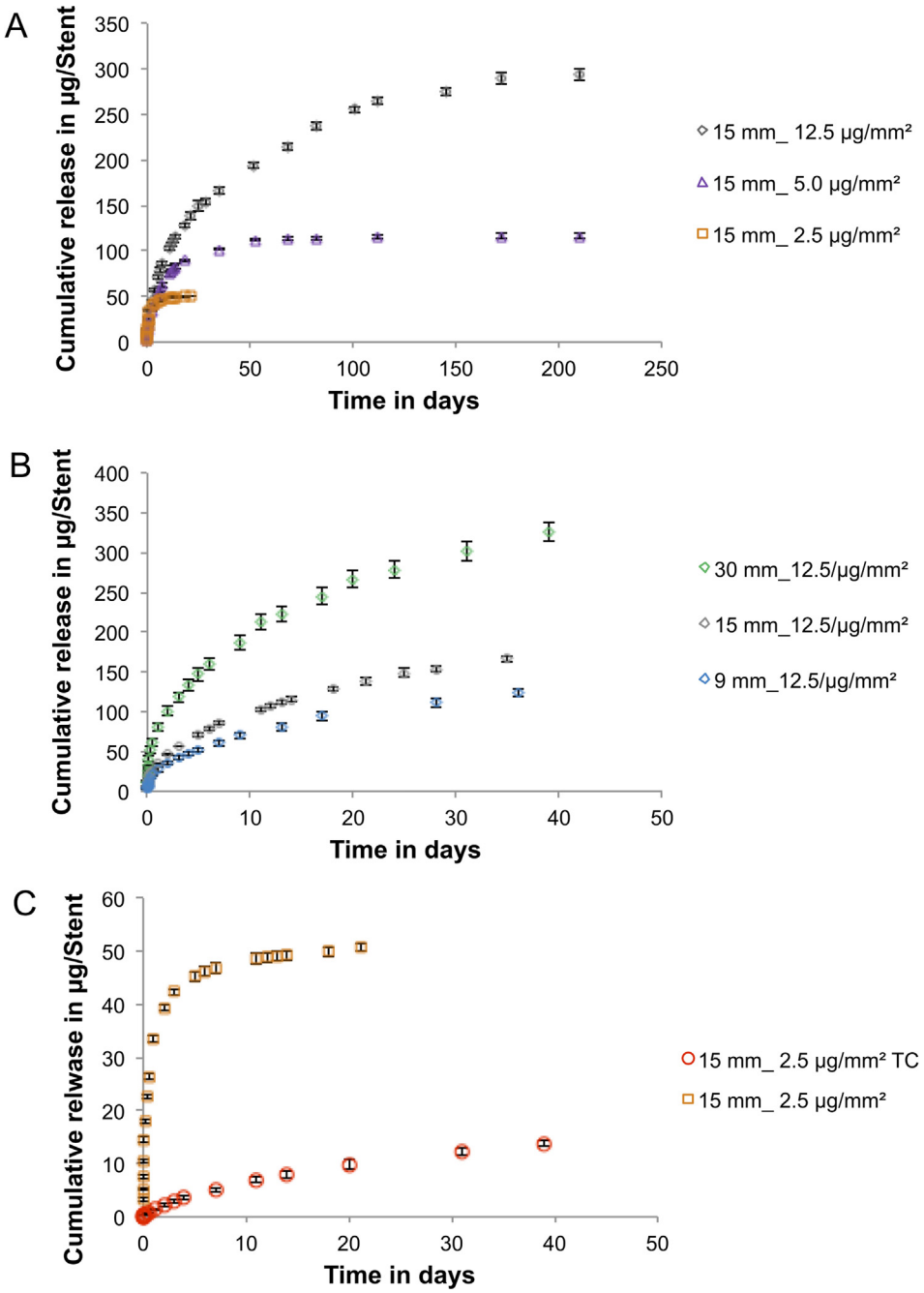

Fig. 6. In vitro release profiles of one selected batch of the different coating approaches, means of n = 4 ± SD, (A) comparison of release from 15 mm stents in dependency of different loadings, (B) comparison of release from stents of different length with high loading, (C) comparison of release from 15 mm stents low loading with or without topcoat (TC).

large quantity of fluidized objects compared to standard stent coating processes. Smooth and form-fitting coatings were obtained and an acceptable uniformity of model drug content was found. Drug release was reproducible within batches and drug releases of up to 200 days were determined in vitro. Drug release was further retarded by adding a "drug-free" topcoat. Further tuning of drug release behaviour may be achieved by varying the ratio of model drug and polymer. In conclusion, fluidized bed coating of stents offers the opportunity for a high-throughput coating of stents with tuneable release properties. Further work will be necessary to transfer the results obtained here to a clinically relevant coating composition.

5. Disclaimer

The data presented here is also part of the doctoral thesis of Monika Wentzlaff (thesis in German, title: Beschichtung von Koronarstents im Wirbelschichtverfahren).

Acknowledgement

The authors thank the shop of the faculty of mathematics natural sciences for the construction of the bottom plate for the fluidized air apparatus. Furthermore, the authors thank Cortronik GmbH and Evonik Industries AG for generously providing raw materials. Technical assistance by Sabine Ristow and Thomas Brand is gratefully acknowledged.

Financial support by the German Federal Ministry of Education and Research (BMBF) within REMEDIS is gratefully acknowledged.
SPITZENFORSCHUNG & INNOVATION IN DEN NEUEN LÄNDERN

References

[1] J.W. Moses, M.B. Leon, J.J. Popma, P.J. Fitzgerald, D.R. Holmes, C. O'Shaughnessy, R.P. Caputo, D.J. Kereiakes, D.O. Williams, P.S. Teirstein, J.L. Jaeger, R.E. Kuntz, Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery, N. Engl. J. Med. 349 (2003) 1315–1323.
[2] G.W. Stone, S.G. Ellis, D.A. Cox, J. Hermiller, C. O'Shaughnessy, J.T. Mann, M. Turco, R. Caputo, P. Bergin, J. Greenberg, J.J. Popma, M.E. Russell, A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease, N. Engl. J. Med. 350 (2004) 221–231.
[3] S. Garg, P.W. Serruys, Drug-eluting stents: a reappraisal, Heart 96 (2010) 489–493.
[4] R. Wessely, J. Hausleiter, C. Michaelis, B. Jaschke, M. Vogeser, S. Milz, B. Behnisch, T. Schratzenstaller, M. Renke-Gluszko, M. Stöver, E. Wintermantel, A. Kastrati, A. Schömig, Inhibition of neointima formation by a novel drug-eluting stent system that allows for dose-adjustable, multiple, and on-site stent coating, Arterioscler. Thromb. Vasc. Biol. 25 (2005) 748–753.
[5] J. Deng, Y. Han, M. Sun, J. Tao, C. Yan, J. Kang, S. Li, Nanoporous CREG-eluting stent attenuates in-stent neointimal formation in porcine coronary arteries, PLoS ONE 8 (2013) e60735.
[6] Y. Wang, W. Zhang, J. Zhang, W. Sun, R. Zhang, H. Gu, Fabrication of a novel polymer-free nanostructured drugeluting coating for cardiovascular stents, ACS Appl. Mater. Interfaces 5 (2013) 10337–10345.
[7] S. Farah, Protective layer development for enhancing stability and drug-delivery capabilities of DES surface-crystallized coatings, ACS Appl. Mater. Interfaces 10 (2018) 9010–9022.
[8] S.F.A. Hossainy, Method for coating an implantable device and system for performing the method, US Patent 6555157B1; 2003.
[9] S.D. Pacetti, Apparatus and method for coating implantable devices, US Patent 7175874B1; 2007.
[10] M. McDermott, S. Chatterjee, X. Hu, A. Ash-Shakoor, R. Avery, A. Belyaeva, C. Cruz, M. Hughes, J. Leadbetter, C. Merkle, T. Moot, S. Parvinian, D. Patwardhan, D. Saylor, N. Tang, T. Zhang, Application of quality by design (QbD) approach to ultrasonic atomization spray coating of drug-eluting stents, AAPS PharmSciTech. 16 (2015) 811–823.
[11] N. Scoutaris, F. Chai, B. Maurel, J. Sobocinski, M. Zhao, J.G. Moffat, D.Q. Craig, B. Martel, N. Blanchemain, D. Douroumis, Development and biological evaluation of inkjet printed drug coatings on intravascular stent, Mol. Pharm. 13 (2016) 125–133.
[12] J. Wang, Y. Ren, Y. Huang, R. Du, Y. Xi, T. Yin, Y. Wang, D. Zhang, J. Chen, G. Wang, An asymmetrical dual coating on the stent prepared by ultrasonic atomization: ADC on the stent prepared by ultrasonic atomization, J. Biomed. Mater. Res. 107 (3) (2019) 825–837, https://doi.org/10.1002/jbm.b.v107.310.1002/jbm.b.34179.
[13] Q. Guo, J.P. Mather, P. Yang, M. Boden, P.T. Mather, Fabrication of polymeric coatings with controlled microtopographies using an electrospraying technique, PLoS One 10 (2015) e0129960.
[14] T. Hu, S. Lin, R. Du, M. Fu, Q. Rao, T. Yin, Y. Huang, G. Wang, Design, preparation and performance of a novel drug-eluting stent with multiple layer coatings, Biomater. Sci. 22 (2017) 1845–1857.
[15] L.C. Su, Y.H. Chen, M.C. Chen, Dual drug-eluting stents coated with multi layers of hydrophobic heparin and sirolimus, ACS Appl. Mater. Interfaces 5 (2013) 12944–12953.
[16] S. Petersen, J. Hussner, T. Reske, N. Grabow, V. Senz, R. Begunk, D. Arbeiter, H.K. Kroemer, K.P. Schmitz, H.E. Meyer zu Schwabedissen, K. Sternberg, In vitro study of dual drug-eluting stents with locally focused sirolimus and atorvastatin release, J Mater Sci: Mater Med 24 (11) (2013) 2589–2600, https://doi.org/10.1007/s10856-013-5001-7.
[17] M. Schwarz, K. Miller, K. Kamath, Coating medical devices using air suspension, European Patent 1171245B1; 2006.
[18] M. Schwarz, J. Weber, H. Hansen, P. Lubinsky, Device for protecting medical devices during a coating process, US Patent 6607598B2; 2003.
[19] J. Niu, J. Haslam, R. Rajewski, B. Subramaniam, A fluidized-bed coating technology using near-critical carbon dioxide as fluidizing and drying medium, J. Supercrit. Fluids. 66 (2012) 315–320.
[20] E. Watanabe, M. Takahashi, M. Hayashi, A possibility to predict the absorbability of poorly water-soluble drugs in humans based on rat intestinal permeability assessed by an in vitro chamber method, Eur. J. Pharm. Biopharm. 58 (2004) 659–665.
[21] R.T. Liggins, W.L. Hunter, H.M. Burt, Solid-state characterization of paclitaxel, J. Pharm. Sci. 86 (1997) 1458–1463.
[22] P. Simamora, J.M. Alvarez, S.H. Yalkowsky, Solubilization of rapamycin, Int. J. Pharm. 213 (2001) 25–29.
[23] N. Grabow, M. Wentzlaff, V. Senz, A. Seidlitz, C. Harder, K. Sternberg, W. Weitschies, K.P. Schmitz, Feasibility of polymer/drug coating on absorbable and permanent stent platforms – technological challenges, Biomed. Tech. 58 (2013) 4383.
[24] S.L. Chen, F. Ye, J.J. Zhang, J.J. Zou, X.S. Qian, F. Li, S. Yang, Z. Ge, S.J. Shan, X.B. Li, T. Xu, J. Kan, L. Lin, Y.L. Han, Real polymer-free sirolimus- and probucol-eluting versus biodegradable polymer sirolimus-eluting stents for obstructive coronary artery disease: DKPLUS-wave 1, a multicenter, randomized, prospective trial, Cardiovasc. Ther. 31 (2013) 193–200.
[25] A. Seidlitz, S. Nagel, B. Semmling, S. Petersen, T. Reske, W. Schmidt, N. Grabow, K. Sternberg, W. Weitschies, In vitro estimation of drug loss during the implantation procedure of drug-eluting stents, Biomed. Tech. 57 (2012) 4120.
[26] A. Dibra, A. Kastrati, J. Mehilli, J. Pache, R. von Oepen, J. Dirschinger, A. Schömig, Influence of stent surface topography on the outcomes of patients undergoing coronary stenting: a randomized double-blind controlled trial, Catheter Cardiovasc. Interv. 65 (2005) 374–380.
[27] M.W. Basalus, K. Tandjung, T. van Westen, H. Sen, P.K. van der Jagt, D.W. Grijpma, A.A. van Apeldoorn, C. von Birgelen, Scanning electron microscopic assessment of coating irregularities and their precursors in unexpanded durable polymer-based drug-eluting stents, Catheter Cardiovasc. Interv. 79 (2012) 644–653.
[28] V. Senz, W. Schmidt, N. Grabow, D. Arbeiter, K. Sternberg, K.P. Schmitz, Coating thickness determination on drug-eluting stents - comparison of methods, Biomed. Tech. 58 (2013) 4082.
[29] A. Seidlitz, S. Nagel, B. Semmling, N. Grabow, H. Martin, V. Senz, C. Harder, K. Sternberg, K.P. Schmitz, H.K. Kroemer, W. Weitschies, Examination of drug release and distribution from drug-eluting stents with a vessel-simulating flow-through cell, Eur. J. Pharm. Biopharm. 78 (2011) 36–48.
[30] A. Seidlitz, W. Schick, T. Reske, V. Senz, N. Grabow, S. Petersen, S. Nagel, W. Weitschies, In vitro study of sirolimus release from a drug-eluting stent: comparison of the release profiles obtained using different test setups, Eur. J. Pharm. Biopharm. 93 (2015) 328–338.
[31] N. Bege, S.O. Steinmüller, M. Kalinowski, R. Reul, S. Klaus, H. Petersen, C. Curdy, J. Janek, T. Kissel, Drug eluting stents based on poly(ethylene carbonate): optimization of the stent coating process, Eur. J. Pharm. Biopharm. 80 (2012) 562–570.