Biomed Tech 2012; 57 (Suppl. 1) © 2012 by Walter de Gruyter · Berlin · Boston. DOI 10.1515/bmt-2012-4167

Coating of collars via fluidised-bed process

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Abstract

Collars are small cylindrical tubes which serve as drug reservoirs that are fitted directly on the lead tip of a pacemaker electrode to reduce inflammatory response after the implantation. Currently, collars are produced by injection moulding which may be associated with content variability and long manufacturing times. Hence, the goal of this study was to adapt the effective fluidised-bed process for coating of collars.

In this study, collars were coated in a fluidised-bed apparatus with Eudragit ®RS 30D as an aqueous dispersion which contained the water-soluble model substance fluorescein-sodium. The process parameters and the composition of coating liquid were adapted to obtain a smooth coating surface. Throughout this investigation the surface morphology of the coated collars was explored by using different microscopic methods. Additionally, the homogeneity of coating content was determined fluorometrically and by differential weighing.

Our findings provide a basis for coating of collars via fluidised-bed technology. The fluidised-bed technology was applicable to produce collars with a microscopic smooth surface and high homogeneity of drug content. Nevertheless, further optimizations of the coating composition are necessary to create a coating which is flexible and robust enough to mount the collar onto the pacemaker lead without causing coating defects.

1 Introduction

The implantation of a pacemaker lead produces a local inflammatory response at the endocardial surface of the heart. This inflammatory response influences the function of the pacemaker by increasing the lead stimulation thresholds. This leads to a decreasing endurance of the pacemaker battery which is associated with an operative procedure to change the pacemaker box with battery. Therefore, the electrode is combined with a polymeric collar containing a steroid to reduce inflammatory response and to prevent the threshold rise. Furthermore, the adjustment of the pacemaker parameters is facilitated due to less threshold fluctuations. The drug-eluting collar (DEC) is placed immediately adjacent to the electrode tip. Consequently, a DEC prevents an early surgical intervention [1-4].

Currently, the active pharmaceutical ingredient is incorporated in collars during its manufacturing via injection moulding technology. However, this may result in drug content variability and long process times. To minimize content variability and manufacturing time the fluidised-bed technology is under examination for the production of collars with high content homogeneity.

The fluidised-bed process is an established coating method used in pharmaceutical, cosmetic and food industries. In galenics, this technology is often used for coating of large amounts of small dosage forms with high uniformity. During fluid bed processing a stream of air or gas passes upwards through the coating goods and sets them into motion so that the particles to be coated are suspended and form a fluidised bed. The coating liquid is sprayed onto the fluidised coating goods which are dried by the airstream while in movement [5, 6].

Compared to conventionally coated objects such as pellets, collars neither show moisture absorption nor friability, the surface is smoother and heat may cause the polymer to expand.

In order to obtain a microscopically smooth and uniform surface the parameters of the fluidised-bed process must be adapted with respect to the material characteristics.

The aim of this work was to produce collars with high homogeneity of surface morphology and of drug content. Furthermore, the coating has to be flexible and robust enough to mount the collar onto the pacemaker lead.

2 Methods

2.1 Experimental design

During these trials the collars were coated in a bottom-spray fluidised-bed process using the Mini-Glatt fluidised-bed apparatus equipped with the Micro-Kit product container and the Wurster bottom plate (Glatt GmbH, Germany).

The coating processes was performed at 0.3 bar process pressure and an inlet air temperature of 80 °C to reach a target product temperature between 55-60 °C.

A batch size of approximately 6 g was used in each trial which corresponds to a volume of 70 mL and almost 6000 individual collars. The totally applied quantity of coating lacquer was approximately 0.8 g per batch.

The collars that served as coating goods consisted of polyurethane. Each collar had a length and outer diameter of approximately 2 mm, a wall thickness of 65 µm and a weight of about 1 mg.

The coating liquid consisted of a copolymer based on ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups (Eudragit ® RS 30 D) [Rhöm GmbH, Germany] dispersed in purified water (content data shown as mass percent in relation to total mass of coating liquid). Furthermore, 5 % (w/w, in relation to coating polymer dry mass) of the water soluble fluorescent model substance fluorescein sodium [Sigma-Aldrich Chemie GmbH, Germany] were added. In one case the plasticizer triacetine (Carl Roth GmbH &Co.KG, Germany) (content data shown as mass percent in relation to coating polymer dry mass) was added.

To obtain smooth surfaces varying process parameters and compositions were tested using different batches as shown in table 1. Depending on the predetermined coating parameters the total duration of the coating process varied, but did not exceed 450 min.

After achieving good results in surface morphology the content homogeneity was determined for batch number nine.

To ascertain the influence of the plasticizer on the flexibility and robustness while mounting the collar to the pacemaker lead collars with and without plasticizer were fitted on a lead-tip-dummy after expansion of the collar with forceps. The dummy was a polymeric rod that was about 1 cm long and had a diameter of 2 mm.

Following the coating process a random sample with a sample size of 50 collars was taken from each batch to determine the surface morphology and coating content where applicable.

Table 1: Coating parameters.

	Variable process parameters	spray rate [g/min]	nozzle orifice diameter [mm]	spray pressure [bar]	Composition of coating liquid	Eudragit ® RS 30 D % [m/m]	Plasticizer % [m/m]
B 1		2.4	0.5	0.7		10	-
B 2		0.8	0.5	0.7		10	-
B 3		1.2	0.5	0.7		1	-
B 4		1.2	0.5	1.1		1	-
B 5		1.2	0.5	1.1		0,5	-
B 6		1.2	0.3	1.1		0,5	-
B 7		1.2	0.3	1.1		1	-
B 8		1.2	0.3	1.1		0.25	-
B 9		1.2	0.3	1.1		0.25	20

2.2 Qualitative and quantitative analyses of coating goods

To asses the surface homogeneity three collars of each batch were investigated by stereo incident light microscopy (SILM, Stemi 2000-C, Zeiss AG, Germany) and scanning electron microscopy (SEM, Phenom, FEI Company, USA).

Homogeneity of coating mass was examined by differential weighing. For this purpose 20 coated collars were weighed (Sartorius SE 2, Sartorius AG, Germany). Subsequently, the coating was removed with acetone and the mass of the dried collars was determined. Alternatively, the fluorescein sodium content was measured fluorometrically (Varioskan Flash, ThermoScientific, USA; λ_{ex} 490 nm, λ_{em} 515 nm). Therefore, 20 collars were eluted once in 10 mL methanol and the drug content of the incubation fluid was determined.

3 Results

3.1 Surface morphology

In different batches the parameters of fluidised-bed coating process and the composition of the coating liquid were adapted to obtain homogeneous surface morphology [Fig. 1].

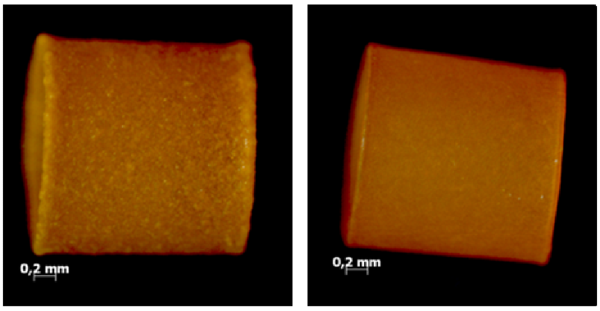

Figure 1: SILM image showing the improvement of surface morphology by adapting the coating parameters, left batch 1 and right batch 9.

During this series of experiments different spray rates were used. As shown in Fig. 2 the homogeneity of the surface decreased with increasing spray rate. Although the surface was still rough it became more uniform using a lower spray rate.

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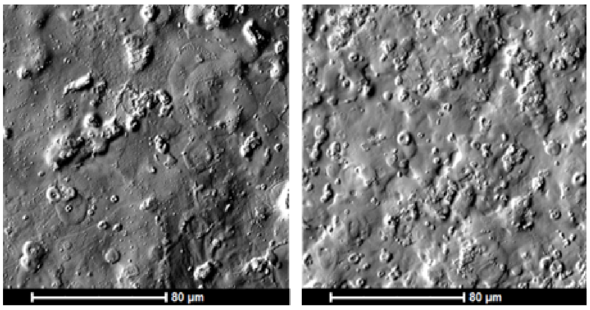

Figure 2: SEM micrographs showing the amendment of surface homogeneity by decreasing the spray rate, left 2.4 g/min (batch 1) and right 0.8 g/min (batch 2).

More homogeneous surfaces were obtained by using a high spray pressure of 1.1 bar [Fig. 3]. Compared with the texture of collars coated with a low spray pressure a smoother surface could be observed.

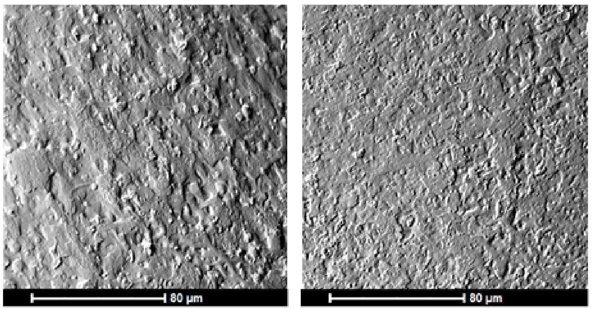

Figure 3: SEM micrographs showing the augmentation of surface smoothness by increasing the spray pressure, left 0.7 bar (batch 3) and right 1.1 bar (batch 4).

With the adjusted spray pressure of 1.1 bar the effect of the nozzle orifice on coating morphology was not that distinct, nevertheless the surface morphology was more uniform when using the nozzle insert with an orifice diameter of 0.3 mm [Fig. 4].

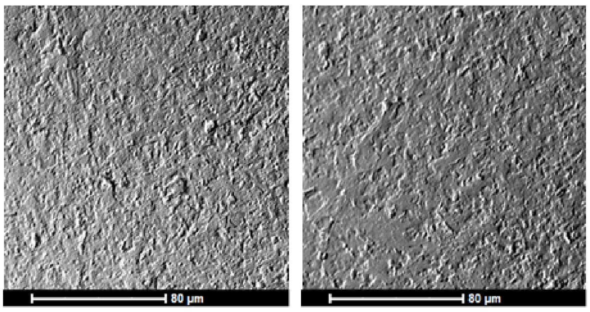

Figure 4: SEM micrographs showing the comparison of resulted coating morphology by using different nozzle orifices, left 0.5 mm (batch 5) and right 0.3 mm (batch 6).

Further optimization of coating liquid composition demonstrated that a lower polymer concentration resulted in a more homogeneous surface morphology [Fig. 5].

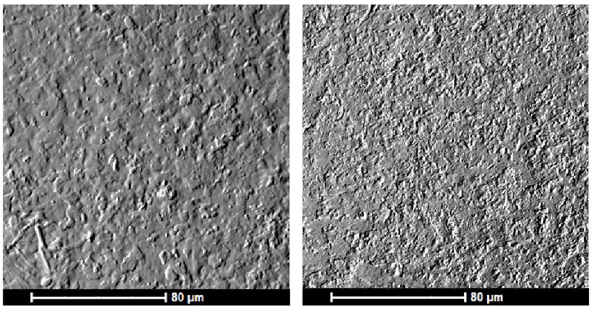

Figure 5: SEM micrographs showing the increase of coating homogeneity after reducing the polymer content of the coating liquid, left 1 % (w/w) (batch7) polymer and right 0.25 % (w/w) (batch 8).

By adding a plasticizer to the low concentrated polymer dispersion the surface roughness was further reduced [Fig. 6].

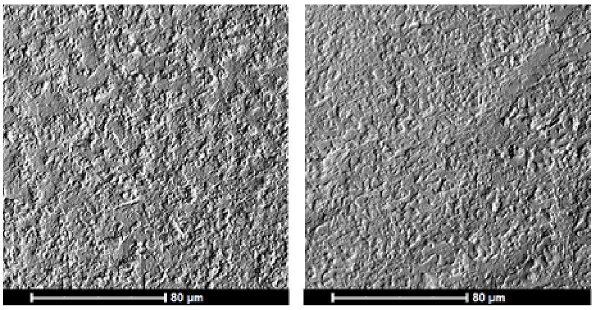

Figure 6: SEM micrographs showing the admixture of plasticizer influenced the surface morphology positively, left without plasticizer (batch 8) and right with plasticizer (batch 9).

Nevertheless, after the application of the collars of batch 8 and 9 (high spray pressure, low polymer content, with or without plasticizer) to the lead-tip-dummy in both cases the coating was damaged, even though the defects seemed to be less pronounced in the formulation containing the plasticizer [Fig. 7].

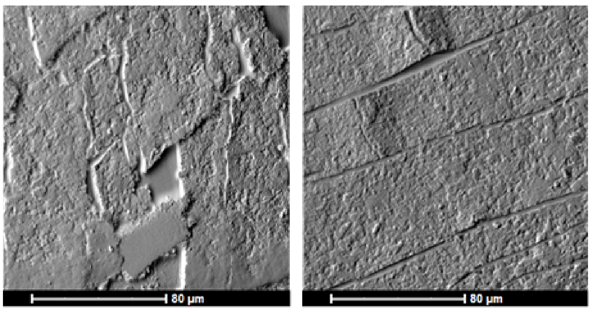

Figure 7: SEM micrographs showing the collar surfaces after mounting onto a lead-tip-dummy, left without plasticizer (batch 8) and right with plasticizer (batch 9).

3.2 Coating content

As a consequence of our findings the homogeneity of coating content was tested with batch number nine.

The distribution of coating layer mass is given in figure 8. The relative standard deviation from the mean was found to be less than 6 %.

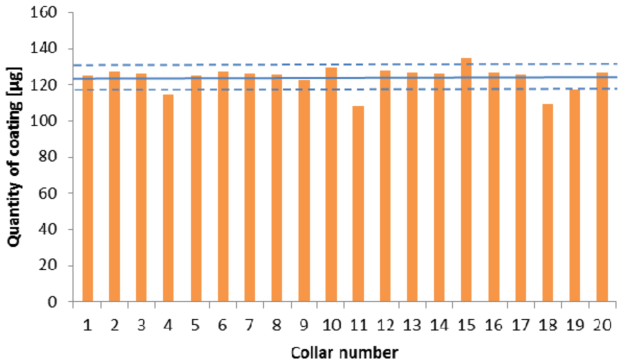

Figure 8: Coating layer mass of different collars, continuous line indicating the mean (123.9 µg), dotted lines indicating the standard deviation (± 5.4 %).

Comparable results were obtained with the fluorometric determination of drug content. Although, part of the fluoresceine sodium diffused into the polyurethane which resulted in incomplete recovery an average fluorescein sodium content of 2.18 µg per collar was detected with a small relative standard deviation of 4.8 %.

4 Conclusion

In summary, the results show that it is possible to coat collars with a high content homogeneity by using the fluidised-bed technology. Despite the high mechanical stress during the coating process, a smooth surface without detectable defects was obtained. However, cracks were detected when mounting the collars on a lead-tip-dummy.
Therefore, in order to obtain more flexible and robust coatings the composition of the coating liquid needs to be further improved.
However, the results provide a sound basis for the development of high-throughput coating processes of collars or similar medical devices with biocompatible polymers.

Acknowledgment

This project was funded by the Federal Ministry of Education and Research (BMBF) within REMEDIS.

SPITZENFORSCHUNG & INNOVATION IN DEN NEUEN LÄNDERN REMEDIS Höhere Lebensqualität durch neuartige Mikroimplantate

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