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Research paper

Solid lipid extrusion with small die diameters – Electrostatic charging, taste masking and continuous production

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ABSTRACT

The aim of this work was to develop a continuous solid lipid extrusion process that includes post-process milling of the extrudates. Die diameters smaller than 0.5 mm should be used for taste masking of the bitter tasting anthelmintic praziquantel. During lipid extrusion with small die diameters, electrostatic charging of the extrudates occured. This could be avoided by adding liquid polyethylene glycol (PEG) as antistatic agent. Further, extrusion with PEG as antistatic agent was possible with small diameter down to 0.2 mm and with up to 80% praziquantel load. Dissolution of praziquantel extrudates was shown to be faster with smaller extrudate diameter due to surface enlargement. Anyhow, different praziquantel extrudates with small diameter, drug load up to 70% and PEG content up to 20%, were proven to be sufficiently taste masked in a randomised palatability study with 40 cats. Within a scale-up experiment, lipid extrusion and milling of the extrudates in a centrifugal mill afterwards were conducted continuously. Extrudates from continuous and batchwise production revealed small differences in terms of size distribution and surface habit, but were similar in drug dissolution rate.

1. Introduction

Recently, in the pharmaceutical industry, more and more efforts are done to replace batchwise by continuous processing. The advantages are time- and cost-efficient scale-up and manufacturing. Development and manufacturing processes can be done on the same equipment, the product volume is easily changed by adjusting the operation time instead of the batch size and quality control is possible online [1]. Extrusion is a continuous process per se, but post-processing of the extrudates in terms of milling, pelletizing or spheronisation is necessary. Therefore, a continuous process from the powder mixture to the pellet would be highly desirable. One solution to this is the Micro Pelletizer LMP (Leistritz, Nürnberg, Germany), which is installed directly at the extruder die plate and continuously cuts extrudates into small pieces. For this method, a die plate is required where the dies are arranged in a circle. This is feasible for die plates with only a few dies and for insensitive processes, where the extrudates leave all dies with the same velocity.

In solid lipid extrusion, a powdered lipid is mixed with a drug and extruded below the melting range of the lipid. The drug is dispersed in the lipid matrix and the lipid does not completely melt but it softens. In previous studies, solid lipid extrusion was used for controlled release systems [2], for protective dosage forms with water-sensitive substances [3,4] and for taste masking of bitter drugs [5]. In these studies, extrudates were post-processed batchwise and the common die diameter was 1 mm. Solid lipid extrusion with a die diameter of 0.3 mm was recently introduced for taste masking purposes [6].

The mechanism of taste masking by solid lipid extrusion becomes apparent on observing the extrudate surfaces. During extrusion, the suspended drug particles evade the resistance of the die plate walls and a thin layer composed of softened lipid is formed on the surface of the extrudates. Cutting or milling the extrudates afterwards also exposes drug particles, whereby some particles lie uncovered on the surface. Dissolution of the drug is enhanced at these uncovered surfaces compared to covered surfaces, where the drug has to diffuse through the thin lipid layer before getting into solution [7]. A cut extrudate is cylindrically shaped and exhibits uncovered surfaces at its two base areas and covered surface at the lateral area. The covered to uncovered surface ratio and therewith the taste masking effect increase with smaller extrudate diameter [6]. Lipid extrudates with small diameter are advantageous particularly for animals. The reasons are not only its taste masking effect, also the adhesion on food is improved; therefore, the animals feel less foreign body sensation and better accept the drug. Additionally, a further processing to tablets or suspensions is easier with smaller extrudate particles. Recently, lipid extrudates

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with 0.3 mm diameter for animals containing the bitter tasting anthelmintic praziquantel were introduced. It was shown that the needle-shaped drug praziquantel has to be milled before extrusion, because needle-shaped particles disturb the process [8,9].

During solid lipid extrusion, electrostatic charging of the extrudates can occur due to friction on the die walls. Particularly, dies with small diameter have large friction surfaces. Since charging increases with the friction surface [10], electrostatic phenomena are likely to appear during extrusion with small die diameters. Electrostatic charging results from contact of two materials. During contact, charge transfer from one material to the other occurs. If one material is a poor conductor or insulator, i.e. a material with high electrical resistivity, it will retain the transferred charge on separation and electrostatic charging results [11].

Static electric problems are unlikely to occur in environments with relatively high air humidity above 60%. This effect is due to a moisture layer on all particles and surfaces, which provides a conductive path for charges to leak away [10]. Besides working in air-conditioned rooms, electrostatic charges can be avoided by adding antistatic agents to a formulation. These materials generally have amphiphilic or hydrophilic structures. Polar groups adsorb sufficient atmospheric moisture to form a surface monolayer [12].

The aim of this work was firstly to overcome electrostatic charging problems during extrusion, secondly to develop a taste masked praziquantel formulation with extrudate diameters smaller than 0.5 mm and thirdly to establish a continuous process with this formulation from powder mixture to post-processed lipid pellets.

2. Materials and methods

2.1. Materials

Praziquantel was obtained from Bayer HealthCare (Leverkusen, Germany) and air jet milled before use. The particle size was $d(0.9)$ 3.6 μm, measured by laser diffraction. The following powdered lipids were received from Sasol (Witten, Germany): glyceryl tripalmitate (Dynasan® 116), glyceryl tristearate (Dynasan® 118) and glyceryl monostearate (Imwitor® 491). Solid paraffin (Sasolwax® 6403) was obtained from Sasol Wax (Hamburg, Germany). Powdered glyceryl dibehenate (Compritol® 888 ATO) and cetyl palmitate (Precifac®) were supported by Gattefossé (Weil am Rhein, Germany). Polyethylene glycol (PEG) was used in molecular weights 1500 and 6000 and was received from Clariant (Sulzbach, Germany), and colloidal silicium dioxide (Aerosil® 200) was acquired from Degussa (Essen, Germany).

2.2. Animals

Healthy, adult cats with body weight from 2.7 to 5.4 kg, owned by Bayer Animal Health (Monheim, Germany), were acclimated to the study facility for at least 7 days prior to the treatment. All experiments were conducted according to European standards for the protection of animals.

2.3. Extrusion

The powdered lipids were mixed with praziquantel in a laboratory scale blender LM 20 (Bohle, Ennigerloh, Germany). All formulations contained 1% colloidal silicium dioxide in order to improve the flowability and precision of dosing. The powder mixture was gravimetrically fed by a dosing device KT 20 (K-Tron Soder, Lenzhard, Switzerland) into the barrel of the co-rotating twin-screw extruder Mikro 27GL-28D (Leistritz, Nürnberg, Germany). The temperature of the extruder barrel was adjusted less than 6 °C below the melting range of the lipid. A constant screw speed of 60 rpm and powder feed rate of 40 g/min were used, except otherwise stated. Die plates with 0.2, 0.25 and 0.3 mm die diameter were used, details are given in Table 1. The pressure in the extruder barrel was measured next to the die plate with a pressure gauge M30-6-M-B35D-1-A-0 XM 281 (Gefran S.p.A., Provaglio d'Iseo, Italy).

2.4. Milling of the extrudates

After cooling down, the extrudates were milled in an ultra centrifugal mill ZM 200 (Retsch, Haan, Germany) with a 12-tooth rotor at 6000 rpm and sieve size 1.5 mm with trapezoid holes. The extrudates were cut cross-sectional into short pieces and afterwards sieved in a sieve shaker AS 200 control (Retsch, Haan, Germany) with 1 mm amplitude for 3 min in order to separate coarse and fine fraction.

During continuous extrusion, a 130 cm long belt conveyor (Brabender, Duisburg, Germany) was used to carry the extrudates directly into the centrifugal mill. The continuously milled extrudates were collected in a downstream cyclone.

2.5. Electrostatic measurements

Electrostatic potential was measured with an electrostatic sensor IZD10-510 with display IZE112 (SMC, Tokyo, Japan), which was placed in front of the extruder 7 cm from the die plate. Sampling rate was one measuring point per second. Temperature and relative humidity were not controlled, but measured during all experiments. Except otherwise stated they were constant at 22 ± 2 °C and 48 ± 2%, respectively. Pulsatile output of the extrudates resulted in fluctuating measurement results; therefore, the average of all data points from the second to the fifth minute of the process was used. The standard deviation is given as a measure of fluctuation.

2.6. Dissolution

Dissolution studies were performed in hydrochloric acid (HCl) pH 1.2 with 0.001% polysorbate 20. The reason for the addition of polysorbate 20 was to improve the wettability of the extrudates, the concentration was set below the critical micelle concentration of polysorbate 20. Closed flow-through-cells apparatus 4 (CE7 smart, Sotax, Switzerland) with tablet cells containing the milled extrudates dispersed in glass beads were used. The flow rate was 16 ml/min. All dissolution experiments were conducted in triplicate. Praziquantel content was determined with ultraviolet detection at 210 nm with one measuring point in 15 min.

The dissolution profiles were compared using the similarity factor f_2. The f_2 value is a number between 0 and 100, and the higher the f_2, the more similar the two compared dissolution profiles are. With a value below 50, the profiles are evaluated as different from each other [13,14].

2.7. Scanning electron microscopy (SEM)

The extrudates were visualised by the scanning electron microscope Leo 1430 VP (Leo Electron Microscopy, Cambridge, UK). The

Table 1
Measures of die plates.

Die diameter (mm)	0.2	0.25	0.3
Number of dies	180	120	67
Die length (mm)	2.5	2.5	2.5
Die length/diameter	12.5	10.0	8.3
Open area (mm^2)	5.7	5.9	4.7

samples were gold sputtered by the Agar Manual Sputter Coater B7340 (Agar Scientific, Stansted, UK) prior to electron microscopic investigations.

3. Results and discussion

3.1. Electrostatic charging

3.1.1. Type of lipid

Solid lipid extrusion with the needle-shaped drug praziquantel is only possible if the drug powder is milled before extrusion, because the needle-shaped particles disturb the process [8,9]. But lipid extrusion of milled praziquantel is still problematic with some lipids that electrostatically charge. Electrostatic charging during extrusion processes causes blocking of dies and extrudates sticking to the outside of the extruder head. This effect particularly occurs during extrusion with die diameters smaller than 0.5 mm. Therefore, electrostatic charging of different lipids during extrusion with praziquantel was investigated in order to find processable formulations for small die diameters.

Glyceryl tripalmitate, glyceryl dibehenate, glyceryl monostearate, cetyl palmitate and solid paraffin were extruded each with 50% praziquantel and 0.3 mm die diameter. Fig. 1 shows the electrostatic potential at the die plate that was measured during the process. Extrudates with glyceryl monostearate and glyceryl dibehenate did not charge electrostatically and no blockade of the dies occured, whereas during extrusion with the other three lipids negative potentials were measured, dies were blocked and extrudates sticked to the outside of the extruder head. With glyceryl tripalmitate, 7% dies were open, expressed as percentage of all dies belonging to the respective die plate, during extrusion with cetyl palmitate, 91% open dies resulted and with solid paraffin 4%. Cetyl palmitate was an exception, because blockade of dies and electrostatic charging did not correlate, nearly all dies were open during the process, although the highest electrostatic potential was measured. Nevertheless, it can be concluded that electrostatic charging during extrusion clearly results in worsening of the process in terms of blocking dies. Secondly, electrostatic charging of the extrudates depends on the type of lipid.

Thomsen et al. [15] investigated different binders for melt granulation in terms of electrostatic charging. They showed that glyceryl monostearate contrary to glyceryl dibehenate is a better binder, because it did not charge electrostatically during the process. The five lipids investigated in this work differ in their number of hydrophilic groups. Glyceryl monostearate and glyceryl dibehenate in contrast to the other lipids are more hydrophilic due to their amount of unesterified hydroxyl groups. Literature values for the electric resistivity of different lipids [16–18] show that lipids have lower electric resistivity with increasing hydrophilic properties from glyceryl monostearate with $10^6\ \Omega$m to paraffin with 10^{14}–$10^{16}\ \Omega$m. Substances with a resistivity above $10^{12}\ \Omega$m are presumed to be insulators, and electrostatic charging occurs if one of two materials in contact is an insulator [10]. It can be concluded that the electric resistivity of a lipid is a measure for its tendency for electrostatic charging during extrusion.

3.1.2. Relative humidity

As described preliminary, static electric problems are unlikely to occur in environments with relatively high air humidity above 60%. This effect is due to a moisture layer on all particles and surfaces that provides a conductive path for charges to leak away [10]. In fluidised bed and melt granulation processes, a strong impact of air humidity on the process has been described [18,19]. The validity of this correlation for lipid extrusion processes was investigated by extruding a cetyl palmitate formulation with 50% praziquantel at different climatic conditions. Compared to the other lipids, this formulation showed the highest electrostatic potential (cf. Fig. 1). In Fig. 2, the results of electrostatic measurements under different climatic conditions are shown. An increase in air humidity from 50% to 58% and 59%, respectively, resulted in a clear decrease in electrostatic charging, but not down to zero. However, this effect did not go along with an increase in open dies during the process. These results confirm that electrostatic charging clearly decreases

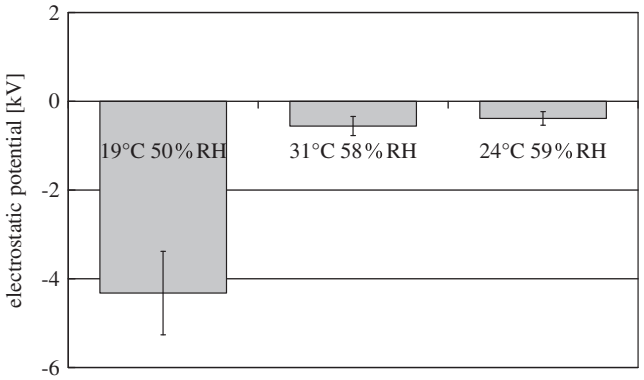


Fig. 2. Influence of relative humidity (RH) on electrostatic charging of 50% praziquantel/49% cetyl palmitate/1% silicium dioxide, mean ± SD.

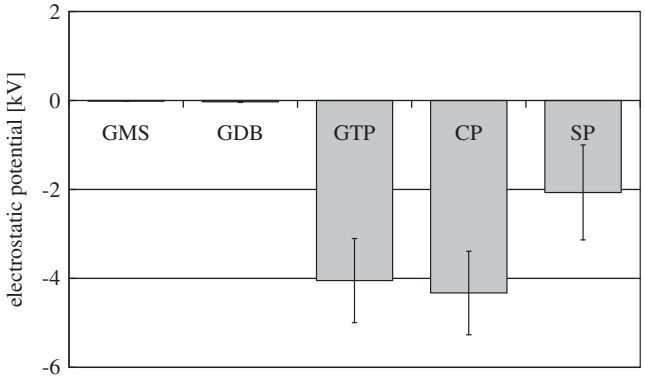


Fig. 1. Electrostatic charging with 50% milled praziquantel and different lipids: glyceryl tripalmitate (GTP), glyceryl dibehenate (GDB), glyceryl monostearate (GMS), cetyl palmitate (CP) and solid paraffin (SP), mean ± SD.

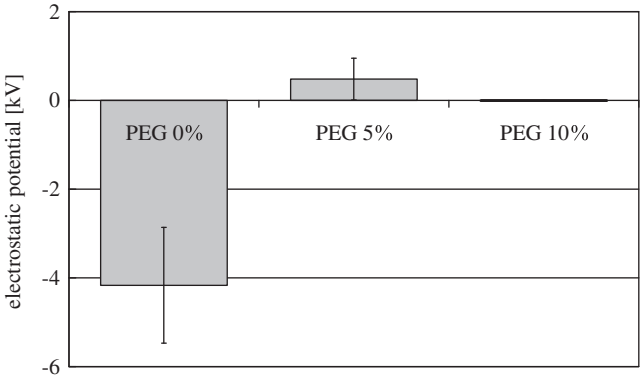


Fig. 3. Electrostatic charging during extrusion with 50% praziquantel/glyceryl tripalmitate (49%, 44% and 39%)/PEG 1500 (0%, 5% and 10%)/1% silicium dioxide, mean ± SD.

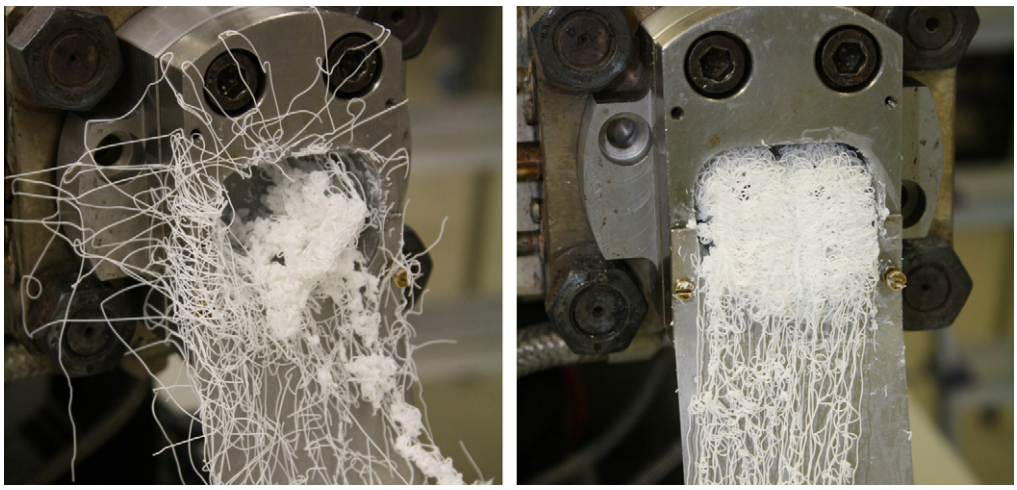


Fig. 4. Pictures of the die plate during extrusion of praziquantel with glyceryl tripalmitate without PEG (left) and with 10% PEG 1500 (right).

at higher air humidity. Presumably, a further increase in air humidity would result in a process with 100% open dies.

3.1.3. Antistatic agent

Besides working in air-conditioned rooms, a possibility to avoid electrostatic charges is adding antistatic agents to a formulation. PEG is a highly water-soluble polymer and has been used previously as antistatic agent for plastics [20,21]. PEG was found to be advantageous compared to lipid binders for melt agglomeration because of its low electrical resistivity and hence its low tendency to electrostatic charging [18]. The suitability of PEG as antistatic agent for solid lipid extrusion was investigated with glyceryl tripalmitate formulations, containing 50% praziquantel using 0.3 mm die diameter. Fig. 3 shows the electrostatic potential that was measured during extrusion with 0%, 5% and 10% PEG 1500. The addition of 5% PEG 1500 resulted in a clear decrease in electrostatic charging compared to the formulation without PEG. Further, a change from negative to positive potential took place. The formulation with 10% PEG 1500 did not show any electrostatic potential at all. The number of open dies during the process increased from 7% without PEG to 10% with 5% PEG and finally to 100% with 10% PEG. Also, the addition of 10% PEG 6000 to a glyceryl tristearate formulation with 50% praziquantel resulted in an increase in open dies from 3% to 100%. Apart from the number of open dies, the addition of 10% PEG 1500 led to a process without visible charging of the extrudates. Fig. 4 shows pictures of the die plate during extrusion with glyceryl tripalmitate and 50% praziquantel without PEG (left) and with 10% PEG 1500 (right). It is clearly visible that charging of the extrudates and sticking to the outside of the extruder head could be avoided with addition of the antistatic agent. These results indicate that the electrostatic potential must be down to zero in order to achieve a process with 100% open dies.

Eliasen et al. [18] investigated PEG with regard to electrostatic charging. They compared different binders for melt granulation processes and found that PEG 3000 was advantageous compared to stearic acid, because of lower electrostatic charging. They concluded that the low electric resistivity of PEG (10^4 Ωm) compared to stearic acid (10^{10} Ωm) might be the reason. Apparently, the electric resistivity of PEG is low enough to convert an insulating lipid into a conductive material.

The antistatic effect of PEG was further investigated at different extrusion temperatures. Fig. 5 shows a process sequence of 20 min with 50% praziquantel/39% glyceryl tripalmitate/10% PEG 6000/1% silicium dioxide and 0.3 mm die diameter. PEG 6000 has a melting point of 60 °C, and glyceryl tripalmitate can be extruded at 52–60 °C. Firstly, the process was run for 8 min at 60 °C, where PEG 6000 melted in the extruder barrel. No electrostatic charging was measured, and the number of open dies was 100%. Afterwards, the barrel temperature was decreased stepwise at first to 55 °C and then down to 52 °C, which is below the melting point of PEG 6000. Directly a positive electrostatic potential was measured, and the number of open dies decreased to 15%. The pressure increase after cooling down was caused by a lower fraction of softened lipid and by blocking dies. It can be concluded that for the antistatic effect of PEG, it is necessary that it is in liquid state during the extrusion process. The activity of an antistatic agent is based on its property to bind a moisture layer on particles and surfaces, which enables charges to leak away. Therefore, it has to be present on the surface of the particle [12]. The reason why the antistatic effect of PEG only occurs in liquid state is probably that only liquid PEG is able to spread through the powder mixture and reach the surface in sufficient quantities. Hence, the selection of an appropriate PEG as antistatic agent for lipid extrusion has to be made according to the melting range of the lipid.

3.2. Extrusion with small die diameter and high drug load

3.2.1. Die diameter

Extrusion with die diameters smaller than 0.5 mm was investigated with a formulation of 50% praziquantel/29% glyceryl tristearate/20% PEG 6000/1% silicium dioxide. Glyceryl tristearate as

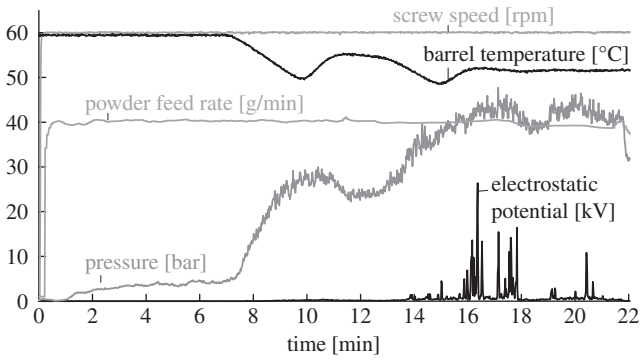


Fig. 5. Process parameter and electrostatic charging during extrusion with 50% praziquantel/39% glyceryl tripalmitate/10% PEG 6000/1% silicium dioxide.

binder was chosen because of its excellent stability [3], PEG was added in the quantity of 20%, because it acts as antistatic agent and additionally as dissolution enhancer. The aim was to analyse whether solid lipid extrusion is possible with die diameters of down to 0.2 mm and to explore the upper limit of possible drug load.

Three different die plates with die diameters of 0.3, 0.25 and 0.2 mm were used. For a comparison of different die plates, it is necessary that the open area, i.e. the area of all dies together, is the same. Therefore, the die plates were designed with an appropriate number of dies (Table 1). The first result concerning the process is that with 50% praziquantel, it was possible to extrude with 0.3, 0.25 as well as with 0.2 mm die diameter. No electrostatic charging was observed, and the process ran with 100% open dies in all cases.

Extrudates of all three diameters were milled in a centrifugal mill, and afterwards a sieve analysis was performed. The sieve fractions were 200–315 μm and 315–400 μm as well as coarse (>400 μm) and fine (<200 μm) fraction. Fig. 6 shows the yield in all investigated sieve fractions. Obviously, with increasing extrudate diameter, coarse fraction gains and fine fraction drops in yield. The main fraction is 200–315 μm for 0.2 mm die diameter with 84% and 0.25 mm with 78% and 315–400 μm for 0.3 mm with 76%. A large scale production of the side fractions makes no sense due to their small yield, but they were also investigated for academical interest.

With sieve fractions 200–315 μm and 315–400 μm of all three extrudate diameters, dissolution testing was conducted (Fig. 7). Obviously, the extrudates with 200–315 μm show a faster dissolution than the extrudates with larger mesh size. This can be explained by the fact that smaller particles have a higher surface area than larger particles, which leads to a faster dissolution of a drug from a matrix according to Higuchi [22]. Similar results have been described by Adeyeye and Price [23], investigating the dissolution of ibuprofen from lipid microcapsules. The extrudates with 0.3 mm diameter and 200–315 μm sieve fraction show the fastest dissolution. For this sieve fraction, the mesh size is smaller than the extrudate diameter; therefore, the majority of the surfaces are uncovered what results in fast dissolution. Comparing the dissolution of the extrudates in their main sieve fractions, the dissolution rate increases with falling extrudate diameter, even though the covered to uncovered surface ratio increases. Obviously, in this case, the effect of over all surface area enlargement on dissolution is predominant. In contrast, Michalk et al. [6] described a slower dissolution for smaller extrudate diameters and give this as advantage for taste masking. This can be explained by the fact that, except the smallest investigated extrudate diameter of 0.3 mm, the mesh size of all sieve fractions

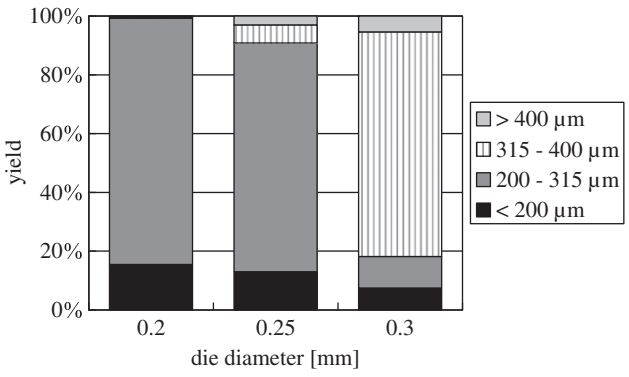


Fig. 6. Yield of extrudates with 0.2, 0.25 and 0.3 mm diameter in different sieve fractions.

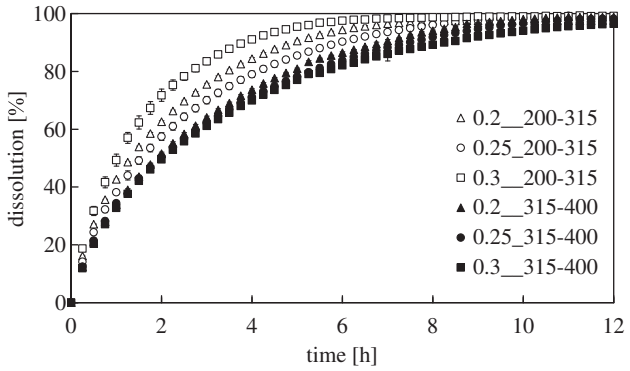


Fig. 7. Drug dissolution of extrudates with 0.3, 0.25 and 0.2 mm diameter, sieve fractions 200–315 μm and 315–400 μm, formulation 50% praziquantel/29% glyceryl tristearate/20% PEG 6000/1% silicium dioxide, mean ± SD (partially covered by symbols).

was smaller than their extrudate diameter. Therefore, the dissolution enhancing effect of uncovered surfaces was predominant for the dissolution results.

Probably a smaller extrudate diameter is also advantageous for taste masking, when the main sieve fraction is used. The enlargement of the overall surface area leads to a faster long time dissolution, but during the short period where the extrudate remains in the mouth, the lipid layer on the extrudate surface avoids drug dissolution. Similar results have been shown with rounded lipid extrudates, where after rounding, the surface is covered with a thin lipid layer [24].

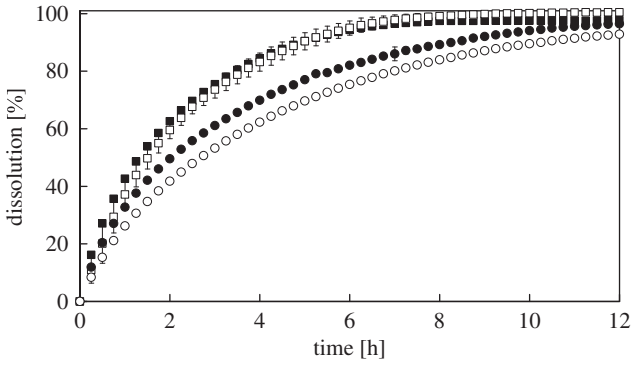
3.2.2. Drug load

A high drug load is advantageous, because the size of a single dosage form can be reduced. Especially, formulations with praziquantel benefit from a high drug load, because of its bitter taste and the necessity of intake of relatively high doses. On the other hand, the higher the drug load, the more the properties of the drug influence the properties of the formulation. Therefore, it is challenging to work with high drug loads, if a drug is difficult to process.

The upper limit of possible drug load was examined for die diameters 0.2 and 0.3 mm. Regardless of praziquantel concentration, the glyceryl tristearate to PEG 6000 ratio was 60:40 in all experiments. Table 2 shows the results of extrusion trials with both die plates. With 0.3 mm die diameter, the upper limit of drug load was 80%; using 0.2 mm dies, it was possible to extrude a formulation with maximum 70% praziquantel. Using higher drug loads with both die plates, the mass accumulated in the barrel, all dies blocked, the pressure inside the barrel increased quickly up to 90 bar and the process had to be stopped. It can be concluded that the upper limit of possible drug load with this formulation is dependent on die diameter. Obviously, the process of solid lipid extrusion is more sensitive the smaller the dies, because the limit of drug load is lower for smaller dies.

Table 2
Percentage of open dies during extrusion with praziquantel and glyceryl tripalmitate to PEG 6000 ratio of 60:40.

Die diameter	50% drug load	70% drug load	80% drug load	90% drug load
0.2 mm	100%	100%	0%	–
0.3 mm	100%	–	100%	0%



symbol	■	□	●	○
die plate	0.2 mm	0.2 mm	0.3 mm	0.3 mm
sieve fraction	200-315 µm	200-315 µm	315-400 µm	315-400 µm
formulation:				
praziquantel	50%	70%	50%	80%
glyceryl tristearate	29%	17%	29%	11%
PEG 6000	20%	12%	20%	8%
silicium dioxide	1%	1%	1%	1%

Fig. 8. Drug dissolution of extrudates with different diameter and drug load, mean ± SD (partially covered by symbols).

The influence of drug load on dissolution rate was investigated with 50% praziquantel loaded samples and extrudates of both diameters each with the highest possible drug load. For both extrudate diameters, the main sieve fraction was used. Fig. 8 shows the detailed composition of all investigated samples and the results of dissolution testing. Dissolution of the samples with 50% praziquantel and different die diameter was already discussed above. The results of dissolution from extrudates with higher drug load show almost no difference between 50% and 70% loaded extrudates with 0.2 mm diameter. The f_2 value for comparison of these two dissolution profiles is 79.8. The extrudates with 0.3 mm diameter show a slightly faster drug release of 50% loaded compared to 80% loaded samples, the similarity factor f_2 is 60.0 in this case.

Typically, in matrix systems, dissolution is faster with higher drug load. According to the percolation theory, a higher drug load in a matrix leads to a denser network of drug particles and therefore to faster dissolution [7,23,25]. These contradictory results can be explained by a closer look at the matrix composition. The higher the drug load was, the smaller the absolute amount of PEG in the formulation was, because the lipid PEG ratio was kept at 60:40 in all formulations (Fig. 8). Instead of 20% PEG in the formulations with 50% praziquantel, the 70% loaded extrudates contained 12% PEG; and formulations with 80% drug contained only 8%. PEG is a hydrophilic polymer that dissolves in water faster than praziquantel, while the lipid matrix remains intact during dissolution. By dissolution of PEG, pores in the matrix occur that either expose the drug to the dissolution medium or shorten the way of diffusion through the lipid matrix [26,27]. It can be concluded that the dissolution enhancing effect of PEG is more pronounced when the amount of PEG in a lipid extrudate formulation is higher. Further, addition of PEG influences the dissolution rate more than increasing the praziquantel load.

3.2.3. Taste masking effect

The taste masking effect of lipid extrudate formulations with small diameter was tested in a randomised palatability study with cats. Cats were chosen as test animals, because they react sensitively to bitter taste and generally reject food that is given together with bitter tasting medicine. Table 3 gives an overview of the tested extrudates. All extrudates contained the drug praziquantel and glyceryl tristearate as matrix former. With four different extrudates, the influence of drug load (II), PEG content (III) and extrudate diameter (IV) on taste masking was tested, each in comparison with test sample I. The acceptability of these four extrudates was examined in forty adult healthy cats as top dressing on dry and canned food.

Table 3
Characteristic parameters of extrudates that were tested in the palatability study.

	I	II	III	IV
Die plate (mm)	0.3	0.3	0.3	0.2
Sieve fraction (µm)	315–400	315–400	315–400	200–315
Formulation (%)				
Praziquantel	50	70	50	50
Glyceryl tristearate	49	11	29	29
PEG 6000	–	8	20	20
Silicium dioxide	1	1	1	1

Forty cats divided into four groups of ten cats each were treated with the usual therapeutic praziquantel dosage of 5 mg praziquantel per kg body weight. The praziquantel dose was offered together with a small amount of dry food in a first study part and in a second study part, 7 days later, together with a small amount of canned food. Palatability assessment was performed by estimation of the medicated food uptake in %. As a second parameter, the uptake of non-medicated food offered immediately after the medicated food was evaluated. The reason was that after having bitter tasting food, cats typically reject following food servings.

The result of the study was that food intake was 100% in all forty cats both with dry and canned food. In conclusion, all extrudates tested were sufficiently taste masked. The dissolution enhancing effect of small extrudate diameters and the addition of PEG did not have a negative influence on the taste masking effect. Even extrudates on canned food were accepted by the cats, although it was likely that the relatively high water content of canned food dissolves bitter tasting praziquantel from the extrudates.

3.3. Continuous processing

Within a scale-up experiment, lipid extrusion with 0.3 mm die diameter and milling of the extrudates in a centrifugal mill

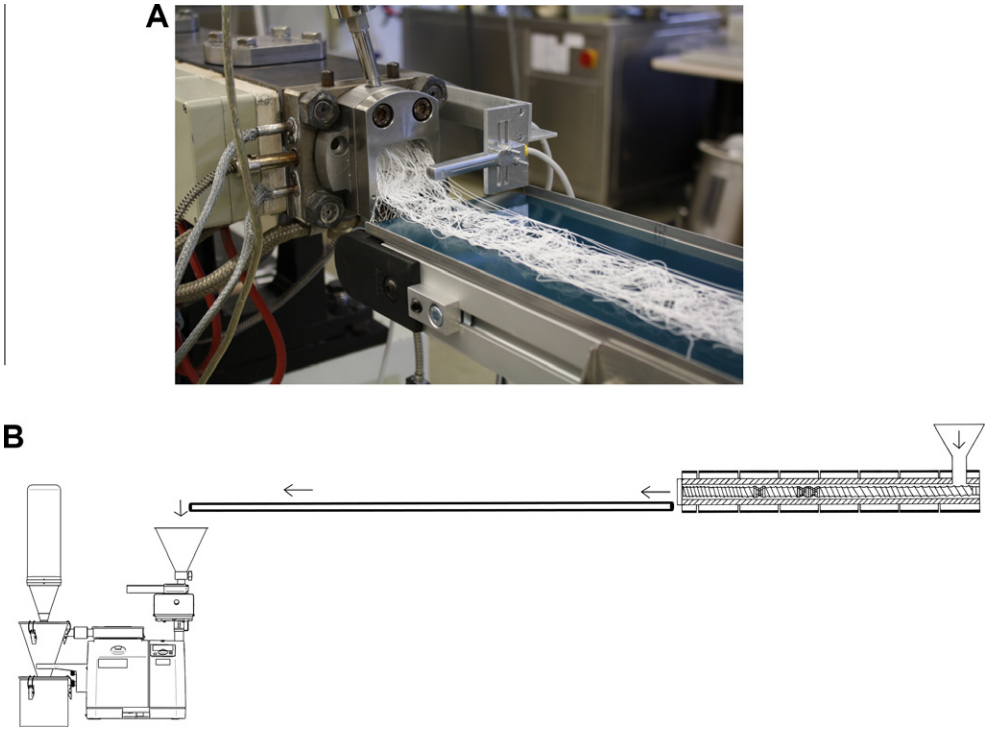


Fig. 9. Picture (A) and schematic (B) of continuous extrusion from Extruder ([28], modified) via a belt conveyor into the centrifugal mill (ZM 200, Retsch, Haan, Germany).

afterwards were conducted continuously. The optimised taste masked formulation with 50% praziquantel/29% glyceryl tristearate/20% PEG 6000/1% silicium dioxide was used in this experiment. Extrudates were carried from the extrusion dies directly into the mill on a belt conveyor. Due to permanent removal, the extrudates did not accumulate or stick together at the die plate (Fig. 9A). During passage of the 130 cm long conveyor, the extrudates had approximately 30 s to cool down (Fig. 9B) and were then continuously milled in a centrifugal mill. In a container with downstream cyclone, the milled extrudates were finally collected.

In this way, the process was conducted for 70 min with a powder feed rate of 40 g/min (2.4 kg/h) and a screw speed of 60 rpm. For further 30 min, the process could be carried out with a powder feed rate of 80 g/min (4.8 kg/h) and a screw speed of 120 rpm. During processing with 80 g/min, however, the milled extrudates were not expelled fast enough from the milling chamber. This resulted in congestion and partial melting of extrudates in the mill. A higher rotor speed entailed a stronger air flow into the cyclone, but again led to higher temperatures in the milling chamber and partial melting of the extrudates. One solution would be an additional external air flow that expels the extrudates from the milling chamber fast enough during high throughput processing.

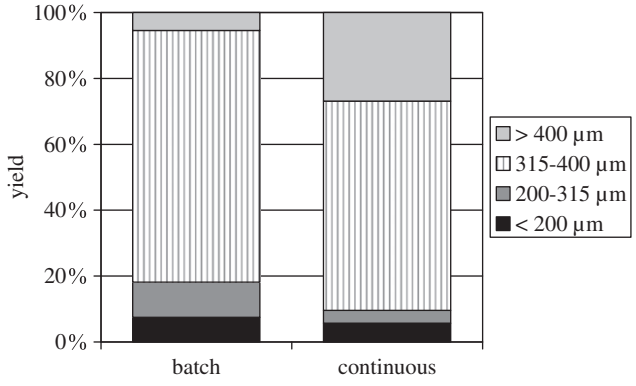


Fig. 10. Yield in different sieve fractions from batchwise and continuous processing.

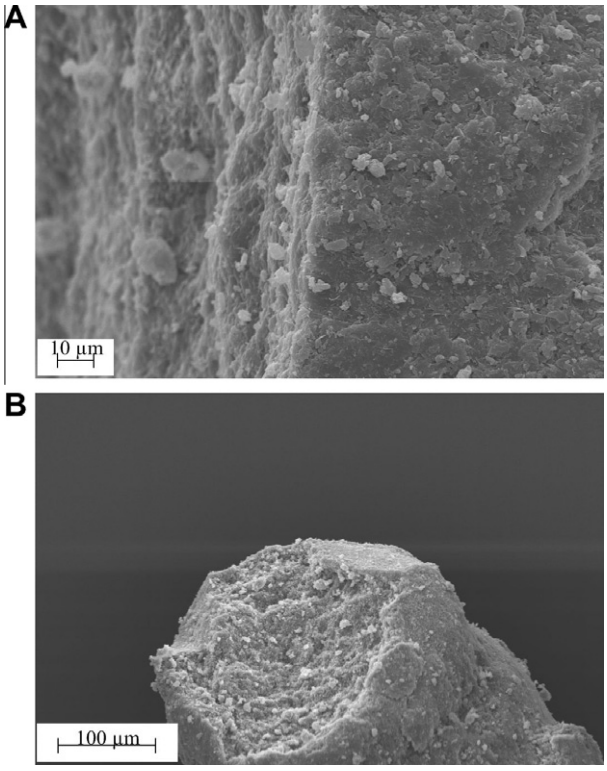


Fig. 11. SEM pictures of extrudates from batchwise (A) and continuous processing (B).

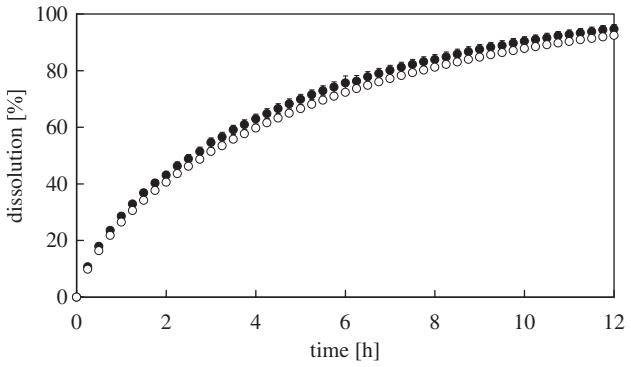


Fig. 12. Drug dissolution with extrudates from continuous (○) and batchwise (●) processing, formulation 50% praziquantel/29% glyceryl tristearate/20% PEG 6000/1% silicium dioxide, mean ± SD (partially covered by symbols).

Extrudates from continuous production were compared to extrudates that were extruded batchwise and milled several hours later in as a post-processing step. In Fig. 10, the results of sieve analysis with extrudates from continuous and batchwise production are shown. The sieve fractions were 200–315 μm and 315–400 μm as well as coarse and fine fraction. The extrudates from continuous production showed a larger coarse and a smaller fine fraction compared to the extrudates from batchwise extrusion. The main fraction of 315–400 μm contained 64% yield with continuous production compared to 76% with batchwise extrusion. Probably during continuous processing, the extrudates did not cool down fast enough and partially agglomerated in the milling chamber. In contrast, during batchwise production, the extrudates had time to completely cool down, because milling was conducted several hours later. With these differences, the larger coarse fraction and smaller yield of continuous produced extrudates can be explained. SEM pictures show right-angled cutting edges of extrudates that were milled several hours after extrusion (Fig. 11A), whereas continuously produces extrudates have flattened cutting edges (Fig. 11B). This also indicates incomplete cooling down of the extrudates during passage to the mill. A longer belt conveyor or a cooling system during passage would ensure complete cool down of the extrudates before milling and probably avoid agglomeration of extrudates in the milling chamber.

Dissolution testing was conducted with extrudates from continuous and batchwise production in order to investigate whether these differences impact the release behaviour. The dissolution rates, which are presented in Fig. 12, show almost no difference with a similarity factor f_2 of 76.7. Consequently, agglomeration of the extrudates during milling effected the extrudate size distribution, but did not impact drug dissolution.

4. Conclusion

Solid lipid extrudates with the bitter tasting drug praziquantel can be produced in a continuous process that includes post-process milling of the extrudates. The dissolution rate is not different between continuously and batchwise produced extrudates. In lipid extrudate formulations, the addition of PEG as pore former and a reduction of the extrudate diameter entail faster drug dissolution. Extrudates with diameters down to 0.2 mm, praziquantel load up to 70% and addition of up to 20% PEG are sufficiently taste masked for administration to cats that react sensitively to bitter taste. During lipid extrusion with small die diameters, electrostatic charging of the extrudates can hinder the process. Liquid PEG in concentrations from 10% acts as antistatic agent and clearly improves the process. The used PEG is chosen according to its molecular weight, being liquid during extrusion and solid after cooling down to room temperature.

In conclusion, an antistatic agent for lipid extrusion was found, taste masked formulations with small extrudate diameters were developed and a continuous process from powder mixture to post-processed lipid pellets was established.

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