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Research paper

Immediate release pellets with lipid binders obtained by solvent-free cold extrusion

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ABSTRACT

Lipid-based drug delivery systems have spread in their use in pharmaceutical drug development. This work focuses on the use of lipid binders as alternative non-toxic extrusion aid for pellet formulations. The preparation of immediate release pellets with solid lipid binders through a solvent-free cold extrusion/spheronisation process was investigated in this study. Various binary, ternary and quaternary mixtures of powdered lipids and the model drug sodium benzoate were investigated and compared to well-known wet extrusion binders like microcrystalline cellulose and κ-carrageenan. The cold lipid extrusion process offers multiple advantages as it is suitable for thermal sensitive as well as for hygroscopic drugs, furthermore no drying process to evaporate the solvent is needed and the process is feasible for different extruder types. Some of the developed pellets showed favourable properties like spherical shape, narrow size distribution, a high drug load of 80% sodium benzoate and a drug release of more than 90% within 40 min. The stability of drug release, which can be problematic when using lipid excipients, was sufficient for some mixtures, as storage under elevated temperatures changed the release profiles only slightly and no formulation released less than 80% within the first 60 min. A formulation with a mixture of hard fat, glycerol distearate and glycerol trimyristate showed the best results, as pellets with a low aspect ratio, narrow size distribution and complete drug release were obtained. Using appropriate mixtures of acylglycerides it becomes possible to produce pharmaceutical pellets with immediate release characteristics by cold extrusion and subsequent spheronisation. Thus, lipids are very promising alternatives to commonly used extrusion/spheronisation binders.

1. Introduction

Lipid-based drug delivery systems are suitable for various drug substances and have spread in their use in pharmaceutical drug development over the last years. They are widely used with poorly water soluble drugs to enhance delivery and bioavailability [1] or as a taste masking agent for bitter tasting drugs [2]. Recently, powdered lipid binders have been investigated as extrusion aids [3] for the solvent-free preparation of pharmaceutical granules [4–6] or pellets [7–9]. In contrast to hot-melt extrusion [10] thermal stress can be decreased due to adjusting the processing temperatures of 10 °C below the melting point of the lipids. This is advantageous for temperature sensitive drugs as well as the binder itself as thermal treatment can influence the stability and morphology. In these cases controlled release, matrix type dosage forms were obtained [5,9,10]. Whereas taste-masked enrofloxacin granules were produced by subsequent milling of the prepared extrudates [5], sustained-release pellets of spherical shape could only be obtained by a spheronisation process at elevated temperatures [9] or melt solidification in drops [11]. In an earlier paper, we used the extrusion/spheronisation process without any heating and introduced the term "cold solvent-free extrusion" [4]. However, the shape of the obtained lipid granules was still cylindrical and not spherical although a spheronisation process was applied. If the granules were left in the spheroniser for a longer time, the lipid melted due to the occurring friction forces and formed aggregates. However, for further processing like film coating or packaging a spherical shape would be advantageous. In general, powdered lipids are assumed to be a desirable alternative in comparison to the most common wet extrusion binders like microcrystalline cellulose (MCC) [12,13] or κ-carrageenan [14], e.g. for drugs unstable in aqueous media or for freely water soluble drugs. An objective of this study was to further explore the cold extrusion process of lipid binders as non-toxic excipients. Sodium benzoate was chosen as the model drug. It is used in rare metabolic diseases like non-ketotic hyperglycinemia [15,16] or hyperammonemia [17]. In most cases, children are affected by these inherited metabolic disorders. Treatment requires high daily doses such as 12 g sodium benzoate per day for a 2-year-old child. Therefore, the drug load of the pellets to be developed should be as high as possible. In our previous study cylindrical and only slightly rounded granules with taste-masking coatings were developed [4]. The aim of this study was to extend the concept of solid lipid extrusion by the variation of

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variables such as lipid composition and process conditions in order to develop immediate release spherical pellets. The pellets with a high sodium benzoate load should show similar properties as traditional pellets made by wet extrusion processes using MCC or κ-carrageenan.

2. Materials and methods

2.1. Materials

The following materials were used in Ph. Eur. Grades: Sodium benzoate from Ethicare GmbH (Haltern am See, Germany); Witocan® 42/44 mikrofein (powdered hard fat) and Dynasan® 114 (glyceryl trimyristate powder) from Sasol GmbH (Witten, Germany); Precirol® ATO 5 (glyceryl palmitostearate powder) and Compritol® 888 ATO (glyceryl dibehenate powder) from Gattefossé GmbH (Weil am Rhein, Germany); κ-carrageenan (Gelcarin® GP911 NF) from FMC (Philadelphia, PA, USA) and microcrystalline cellulose (MCC Sanaq® 102 G) from Pharmatrans Sanaq (Basle, Switzerland).

Benzoic acid RS (USP 05500), lot. F-5, was used as the primary reference standard for all the measurements of sodium benzoate contents and concentrations.

2.2. Extrusion and spheronisation

After weighing, the dry powders were blended for 15 min in the laboratory scale blender LM 40 (Bohle, Enningerloh, Germany) and then transferred to the gravimetric powder feeder of the twin-screw extruder Mikro 27GL-28D (Leistritz, Nuremberg, Germany). The extruder was equipped with an axial screen with 23 dies of 1 and 2.5 mm length. The extrusion of lipid mixtures was performed at a constant screw speed of 50 rpm and a powder feed rate of 40 g/min. Batches of 300 g extrudate were collected and then spheronised at 1500 rpm for 15 min in the spheroniser RM 300 (Schlüter, Neustadt, Germany) fitted with a cross-hatched rotor plate of 300 mm diameter.

With MCC and κ-carrageenan, the extrusion was performed at a constant screw speed of 100 rpm, a powder feed rate of 33 g/min and a suitable liquid supply. The granulation liquid was deionised water continuously pumped by a membrane pump (Cerex EP-31, Bran und Lübbe, Norderstedt, Germany), with a flow through metering device (Corimass MFC-081/K, Krohne, Dusiburg, Germany). Three hundred grams of wet extrudates was spheronised for 5 min at 1000 rpm. The drying step was performed in the fluid bed apparatus GPCG 1.1 (Glatt, Dresden, Germany) for 10 min with an inlet air temperature of 60 °C.

The composition of the investigated formulations is displayed in Table 1.

2.3. Loss on drying

For the determination of the extrudate water content, three samples were taken from each batch produced with wet extrusion. The samples were dried at 70 °C for 24 h in a vacuum oven (Heraeus VT 6060, Kendo, Hanau, Germany). The water of the extrudates was calculated based on dry mass.

2.4. Image analysis

Each batch was sieved from 0.63 to 2.0 mm defining this fraction as yield. Representative samples of suitable volume were obtained from the yield using a rotary cone sample divider (Retschmühle PT, Retsch, Haan, Germany).

Image analysis was conducted using a system consisting of a stereomicroscope (Leica MZ 75, Cambridge, UK), a ring light with cold light source (Leica KL 1500, Cambridge, UK), a digital camera (Leica CS 300 F, Cambridge, UK) and a computer with data logging card and the software Image C (QWin, Leica, Cambridge, UK). Images of at least 500 pellets of each sample at a suitable magnification (1 pixel = 17 μm) were translated into binary images. Contacting pellets were separated by the software algorithm. If the automatic separation failed, pellets were deleted manually. For each pellet, 64 independent Feret diameters were determined, and the projected pellet surface was used to calculate the equivalent diameter for size characterisation. As a method to characterise the shape of the obtained granules, the aspect ratio was used. The aspect ratio was calculated from:

$$AR = \frac{d_{max}}{d_{90}} \quad (1)$$

with maximum Feret diameter (d_{max}) and the Feret diameter perpendicular to it (d_{90}). The pellet size and shape were characterised by mean Feret diameter and aspect ratio.

The ratio of the mean Feret diameter (d_F) and the median of all mean Feret diameters (d_{F50}) was used to calculate the dimensionless particle size (d). The distribution of the particle size was characterised by the fraction of the particles in the interval $0.9 < d < 1.1$.

The size distribution was characterised by Kleinebudde and Thommes as "good" if the fraction of the 10% interval exceeds 50% and as "excellent" if it exceeds 75% [18].

2.5. Drug release

The dissolution tests were performed using the Ph. Eur. basket apparatus method at 150 rpm (Sotax AT7, Sotax, Lörrach, Germany). Preliminary investigations revealed no significant influence of the basket speed on the dissolution profile (50–150 rpm), but 150 rpm was used as a hydrodynamic stress condition. The dissolution media were purified water and phosphate buffer solution

Table 1
Composition of the investigated formulations

Formulation	Sodium benzoate [%]	Benzoic acid [%]	Witocan 42/44 [%]	Compritol 888 ATO [%]	Dynasan 114 [%]	Precirol ATO 5 [%]	Other binders
W20	80		20				
W15 C5	80		15	5			
W15 D5	80		15		5		
W15 P5	80		15			5	
W15 C2.5 D2.5	80		15	2.5	2.5		
W15 P2.5 C2.5	80		15	2.5		2.5	
W15 P2.5 D2.5	80		15		2.5	2.5	
Carrageenan	80						κ-Carrageenan
MCC	80						MCC
Carrageenan BA		80					κ-Carrageenan
MCC BA		80					MCC

W, Witocan 42/44; P, Precirol ATO 5; D, Dynasan 114; C, Compritol 888 ATO.

pH 6.0 R2 (Ph. Eur) continuously pumped (Sotax piston pump CY 7, Sotax, Lörrach, Germany) to a UV/VIS-Photometer (Lambda 2, Perkin–Elmer, Überlingen, Germany). The phosphate buffer pH 6.0 was selected from chapter 2.9.25 Eur. Ph. "Dissolution test for medicated chewing gums" to simulate drug release in the oral cavity. The concentration of sodium benzoate in the dissolution fluid was determined by measuring the absorption at 273 nm. Preliminary investigations showed that the extrusion aids do not have an impact on the absorption at the wavelength 273 nm. All experiments were conducted with five replicates.

2.6. Scanning electron microscopy

Pellets were visualised by the scanning electron microscope Leo 1430 VP (Leo Electron Microscopy, Cambridge, UK). The samples were gold sputtered by the Agar Manual Sputter Coater B7340 (Agar Scientific, Stansted, UK) prior to electron microscopic investigations.

2.7. Stability testing

Storing at accelerated conditions was performed in a Heraeus UT-6060 (Kendo, Hanau, Germany). The lipid pellet batches were stored at 40 °C for 30 days.

2.8. HPLC

Sodium benzoate or benzoic acid content from MCC and κ-carrageenan extrudates was determined by a validated high-performance liquid chromatography (HPLC) method, described by Breitkreutz [4]. An extrudate sample equivalent to 50 mg benzoic acid or 60 mg sodium benzoate was completely dissolved in 100 ml distilled water in a volumetric flask; 5.0 ml of the solution was diluted to 100 ml with the HPLC eluent, a mixture of 30% acetonitrile and 70% 0.01 M aqueous ammonium acetate solution adjusted to pH 4.5 by acetic acid. Twenty microliters of the solution was injected into the HPLC apparatus Hewlett-Packard 1090 Series II (Agilent, Böblingen, Germany) adjusted to 40 °C, equipped with a reverse phase prepacked column Agilent Eclipse XDB-C18 (dimensions: 4.6 × 150 mm, size of packaging material: 5 μm, Agilent) and an UV-diode array detector. Flow rate was 1.0 ml/min. The sodium benzoate content was calculated by the area under the curve of the clearly resoluted absorption peaks at a retention time from 3.7 to 3.8 min compared to external calibration standards of the pure drug treated in the same manner. The content was determined for six samples per batch. Drug content was determined for each pellet batch obtained by wet extrusion to assess the loss of volatile benzoic acid during the drying step. The solid lipid extrusion process ensures a stable and uniform content of sodium benzoate in both the extrudates and the pellets. Preliminary investigations revealed that there is no loss of the active ingredient.

2.9. Differential scanning calorimetry (DSC)

Thermal characteristics of the powdered lipids were studied using a Mettler DSC 821e (Mettler Toledo, Giessen, Germany). DSC scans were recorded at a heating rate of 10 °C/min. Samples with an initial weight of approximately 3 mg were heated from 20 to 120 °C in a sealed and pierced aluminium pan. An empty aluminium pan was used as reference.

3. Results and discussion

In our previous study, the granules with 80% sodium benzoate and 20% Witocan 42/44 as the lipophilic binder were produced at room temperature using a rotary die press without heating segments [4]. The spheronisation had to be stopped after 5 min at 900 rpm rotating speed as the granules started to melt due to the occurring friction forces. The shape of the obtained granules was cylindrical with smoothed edges, but not spherical. The aim of this study was to optimize the existing formulation in order to achieve spherical pellets by varying process and formulation factors.

3.1. Production of pellets through an extrusion/spheronisation process

Our experimental requirements for the extrusion process included a high drug load and a robust extruder configuration, which comprised a simple screw set-up and extrusion at room temperature without thermal treatment of the formulations, to allow an easy equipment change. The previous formulation with 80% sodium benzoate and 20% Witocan 42/44 was taken as the reference and changed by replacing parts of the binder with one or more lipids resulting in binary, ternary and quaternary powder mixtures. After blending the drug substance with the excipients, the powder mixture was fed to the twin-screw extruder. The extrusion process was found to be very robust. None of the tested formulations showed any problems during extrusion and therefore the initial settings remained unchanged. Under the process conditions the extrusion aids could not melt. The different melting points of the chosen lipids are shown in Table 2. Typical DSC curves with the melting peaks of the powdered lipids are displayed in Fig. 1. Hence, binding of the drug substance was achieved by softening or melting of small parts of the binder, but not by thorough melting of the excipients. The critical process step with these lipid formulations proved to be the spheronisation process. To find the optimal spheronisation parameters for obtaining spherical pellets, the basic formulation consisting of 80% SB and 20% Witocan 42/44 was spheronised at different temperatures, with different rotating speeds and for different time intervals. Temperatures more than 15 °C below the melting point of the binder as well as temperatures closer than 8 °C to it proved to be insufficient for the production of suitable shaped pellets. In this case, a spheroniser temperature of 10 °C below the melting point of Witocan 42/44, i.e. 33 °C, revealed the best results.

3.2. Pellet properties

Various parameters are used to characterise the shape of pellets as a quality property [19,20]. The parameter most commonly used is the aspect ratio (AR), which was also used in our investigations and displayed in Figs. 2, 3 and 5. A mean aspect ratio lower or equal to 1.2 was considered as sufficient for pharmaceutical pellets. Aspect ratios above that value were regarded as insufficient [21]. The influence of spheronisation time and friction plate speed is displayed in Fig. 2. An increase in time of spheronisation and an elevated speed of the friction plate resulted in lower aspect ratios. Resulting from these findings further spheronisation for all batches was set to 1500 rpm, the highest possible speed of the spheroniser, for 15 min at 33 °C. Higher temperatures led to the melting of the lipids and subsequently the agglomeration of pellets. In a further step, the type and amount of binders were varied. To compare lipid mixtures to the commonly known extrusion aids MCC and κ-carrageenan the experiments included wet extrusion methods. Furthermore, the therapeutically administered sodium benzoate was replaced by benzoic acid which is regarded as therapeutically equivalent and offers the advantage of reducing the sodium burden for the affected children who often suffer from hypernatremia. As seen in Fig. 3, appropriate spherical pellets with AR < 1.2 could be obtained with MCC, some mixtures of lipids and by changing the active ingredient from salt to the acid form. The previously developed granules made from Witocan 42/44 display the highest

Table 2
Used lipid grades, their composition and characteristics

	Witocan® 42/44 "Hard fat"	Dynasan® 114 "Glycerol trimyri state"	Precirol® AT0 5 "Glycerol distearate"	Cornpritol® 888 ATO "Glycerol dibehenate"
Quality	Ph. Eur.	Food grade	Ph. Eur.	Ph. Eur.
Composition	90% < Triglycerides	95% < Triglycerides	25–35% Triglycerides 40–60% Diglycerides 8–22% Ivlonoglycerides	21–35% Triglycerides 40–60% Diglycerides 13–21% Ivlonoglycerides
Melting point	42–44 °C	55–58 °C	53–57 °C	69–74 °C
HLB	2	2	2	2
Hydroxyl number	15	10	100	100
Batch number	106016	512158 402156	34196	106052
Supplier	Sasol, Witten, Germany	Sasol, Witten, Germany	Gattefosse, Weil am Rhein, Germany	Gattefosse, Weil am Rhein, Germany

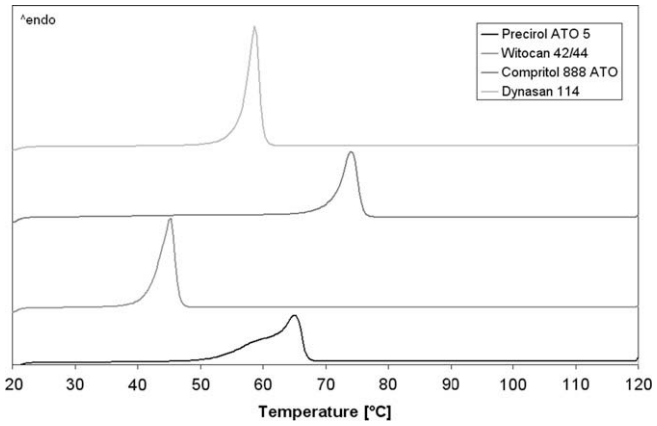

Fig. 1. DSC measurements of untreated lipid powders.

AR with the broadest distribution of particle size and shape. The difference between the κ-carrageenan batches with sodium benzoate and with benzoic acid can be explained by the fact that κ-carrageenan strongly interferes with the sodium ions, which effects the gel forming capacity [22]. Even though benzoic acid proved to be superior to sodium benzoate in terms of the roundness of the pellets and the narrow size and shape distributions, it proved to be inappropriate due to its high vapour pressure. During the drying step which is needed for the wet extrusion process, benzoic acid partly vaporises and the resulting pellets display sponge-like structures, whereas pellets with a lipid binder have a smoother surface, but are harder to shape into ideal round pellets (Fig. 4). Uniformity of dosage units (Ph. Eur. 2.9.40) was not achieved and therefore benzoic acid was rejected for the subsequent studies.

The comparison of the general methods, cold solvent-free solid lipid extrusion and traditional wet extrusion, shows that it is much easier to produce spherical pellets with the classical wet extrusion techniques. However, mixtures of lipids show promising features as they are non-toxic excipients with a GRAS status [23] and no limitations concerning the acceptable daily intake (ADI) levels. The powder mixtures with acylglyceride binders can be extruded at room temperature in a dry extrusion process. A subsequent drying process is not needed in contrast to the wet extrusion process. This is especially important for temperature sensitive active pharmaceutical ingredients and volatile compounds. Furthermore, no solvents are required which makes the process feasible for drug substances sensitive to degradation and pseudopolymorphism. The pellet and batch characteristics for all produced formulations are given in Table 2. The equivalent diameter for lipid pellets ranges from 0.89 to 1.65 mm, whereas the formulations with MCC and κ-carrageenan range from 1.1 to 1.47 mm. Next to the size and shape of pellets another important property for the pellet quality is a narrow particle size distribution. The 10% interval is used to describe the particle size distribution which is based on the dimensionless diameter. It contains the fraction of pellets with-

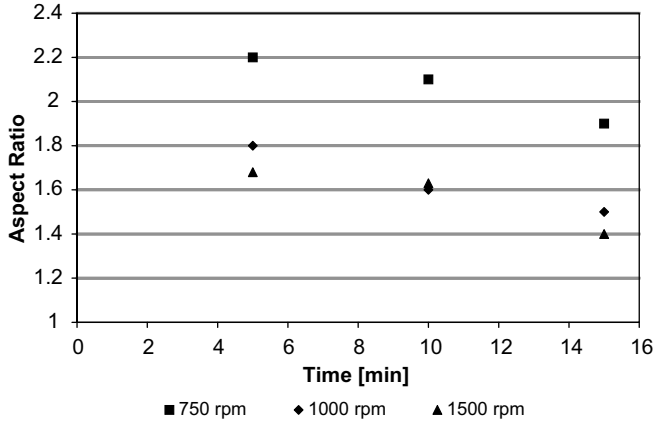

Fig. 2. Influence of spheronisation time and speed on the median aspect ratio of a pellet formulation with 80% sodium benzoate and 20% Witocan 42/44 at a temperature of 33 °C.

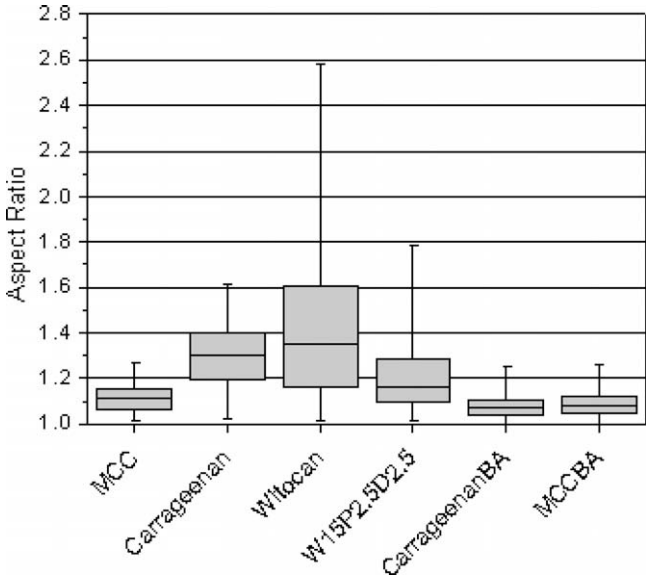

Fig. 3. Pellet shape of different formulations (x_1, x_{25}, x_{50}, x_{75}, x_{99}, $n > 500$) for pellets made by solvent-free solid lipid extrusion and conventional wet extrusion. W, Witocan 42/44; P, Precirol ATO 5; D, Dynasan 114; BA Benzoic acid. Numbers indicate the percental fraction of the lipid in the formulation.

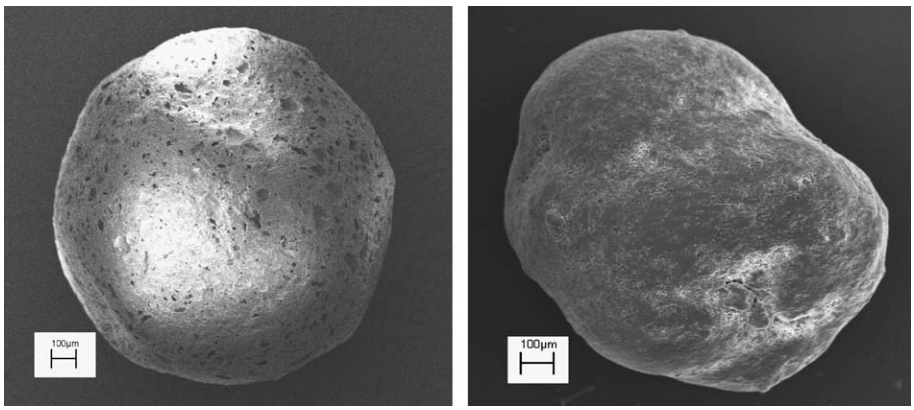

Fig. 4. Scanning electron micrographs of a dried pellet with 80% benzoic acid and 20% MCC (left) and 80% sodium benzoate, 15% hard fat and 5% glycerol dibehenate. Scale bar represents 100 µm.

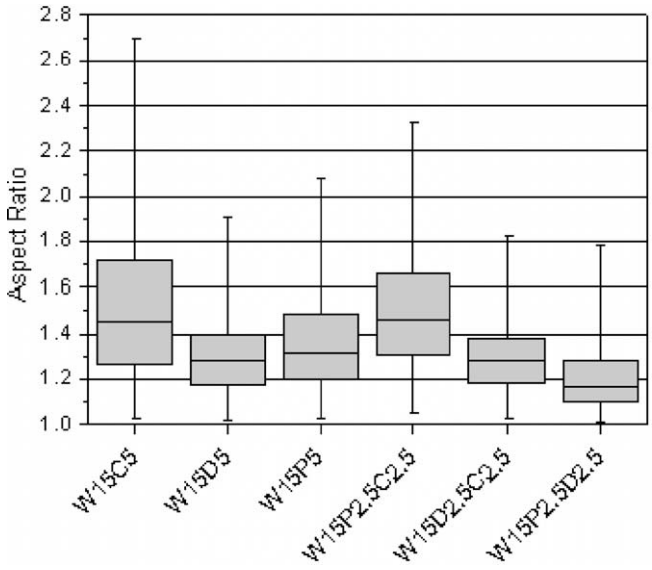

Fig. 5. Pellet shape of different lipid formulations (x_1, x_{25}, x_{50}, x_{75}, x_{99}, $n > 500$) W, Witocan 42/44; C, Compritol ATO 888; P, Precirol ATO 5; D, Dynasan 114. Numbers indicate the percental fraction of the lipid in the formulation.

in the 0.9–1.1 interval of the dimensionless diameter. This fraction can be calculated for all formulations and is independent from the production method thus allowing a batch-to-batch comparison. For the batches with lipids as a binder only three formulations exceeded the 50% limit and therefore rated as "good". This coincides with the three lowest aspect ratios which all are below 1.3. Only one batch displays an AR < 1.2, and therefore the combination of 15% Witocan 42/44, 2.5% Dynasan 114 and 2.5% Precirol ATO 5 is assumed to be the best formulation regarding particle size distribution and shape. It is close to the pellets made from MCC or κ-carrageenan by wet extrusion. In Fig. 5, the aspect ratios of the pellets made from binary and ternary mixtures of different lipids are displayed. Regarding binary mixtures of 15% Witocan and 5% of another lipid, it can be seen that the high melting point of Compritol has a negative effect on the sphericity of the pellets as these pellets display high AR and a broad particle size distribution, the same applied to the ternary mixture with 2.5% Precirol ATO 5 and 2.5% Compritol 888 ATO. The addition of Dynasan 114 led to the three formulations with the lowest AR. It can be concluded that lipids with a lower melting range such as Dynasan (55–58 °C) are favourable in the spheronisation process for the production of spherical pellets as less energy – either through frictional forces or through heating of the spheroniser wall – is needed for the partial melting of the binder which leads to the formation of spheres.

The batches of sodium benzoate with MCC and also with benzoic acid and κ-carrageenan (Table 2 and Fig. 3) were included in the dissolution studies as a reference, but they were not regarded as a therapeutic alternative. As the prescribed doses of sodium benzoate are extremely high – 250–750 mg/kg BW per day – only those substances can be used as excipients which are recognised as safe in almost all doses [4]. The database of food additives [23] evaluated by the World Health Organization (WHO) limits the acceptable daily intake (ADI) for κ-carrageenan as 75 mg/kg BW. This means that, even without calculating special paediatric safety

Table 3
Pellet and batch properties of different formulations

Formulation	Equivalent dia. (mm)	Loss on drying	Yield 0.63–2.0 mm (%)	10% interval (%)	Aspect ratio
W15 C5	0.94 ± 0.22	–	98	43	1.46
W15 P5	1.42 ± 0.33	–	97	43	1.31
W15 D5	1.65 ± 0.21	–	99	72	1.28
W15 C2.5 D2.5	0.89 ± 16	–	98	53	1.29
W15 P2.5 C2.5	1.45 ± 0.33	–	97	45	1.46
W15 P2.5 D2.5	1.61 ± 0.32	–	98	66	1.16
W20	0.96 ± 0.21	–	98	44	1.31
Carrageenan	1.47 ± 0.24	41.72 ± 0.49	96	60	1.3
MCC	1.42 ± 0.15	37.91 ± 0.35	98	80	1.11
Carrageenan BA	1.25 ± 0.19	92.22 ± 2.83	99	59	1.07
MCC BA	1.10 ± 0.27	54.99 ± 2.21	99	42	1.08

W, Witocan 42/44; P, Precirol ATO 5; D, Dynasan 114; C, Compritol 888 ATO; BA, Benzoic acid.
Numbers indicate the percental fraction of the lipid in the formulation.

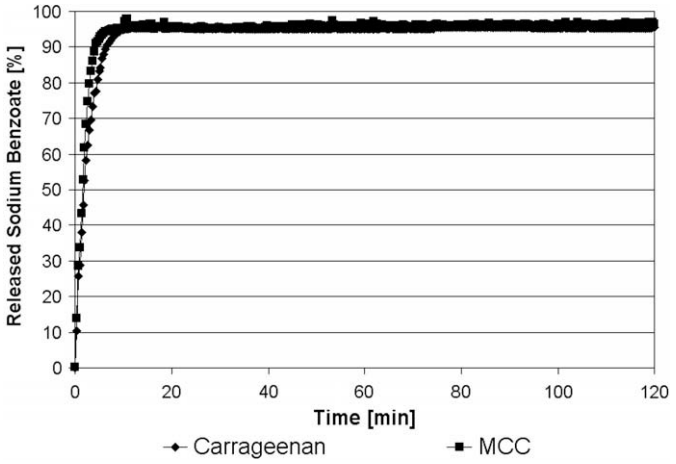

Fig. 6. Sodium benzoate release from pellet formulations. Dissolution media: purified water (arithmetic mean, $n = 6$), temperature: 37 ± 0.5 °C, SD < 3%.

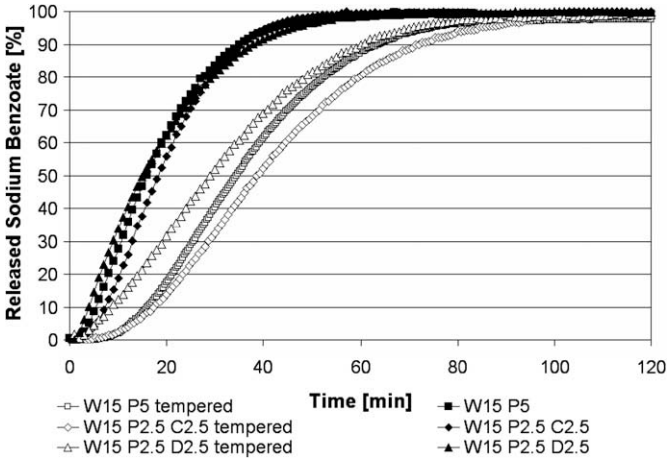

Fig. 8. Influence of storage under accelerated conditions on release characteristics of sodium benzoate pellets. Dissolution media: purified water (arithmetic mean, $n = 6$), temperature: 37 ± 0.5 °C, SD < 4%.

margins, the highest possible dose of sodium benzoate would be 300 mg/kg body weight per day, which in some cases is less than half of the required daily dose. In contrast, MCC has no limitations for ADI, but can be absorbed in the intestinal tract through persorption [24,25]. It is assumed that the persorption rates are elevated in children. The elaborated lipid mixtures are advantageous excipients with low safety concerns and pellet characteristics comparable to the classical extrusion aids (see Table 3).

3.3. Dissolution studies

The release of sodium benzoate from all developed pellet formulations into purified water and phosphate buffer pH 6 was tested according to the Ph. Eur. basket method. As release profiles were almost the same in both media, only release profiles in purified water are displayed. Whereas in Fig. 6 the immediate release of sodium benzoate from batches with MCC and carrageenan can be seen, in Fig. 7 the release from different batches with various lipid binders is presented. It is obvious that due to the lipid nature of the extrusion aids, the release is modified compared to the pellets made by wet extrusion. Nevertheless, all batches released more than 90% in less than 2 h. There is no clear definition for immediate-release dosage form neither in the Ph. Eur. nor in the USP. A suitable range would be the release of at least 80% in 60 min, if this is applied to the release from the presented lipid pellets, all formulations except one, the combination of Witocan 42/44, Precirol ATO 5 and Compritol 888 ATO, would comply to this definition.

The reasons for the rapid drug release, compared to the recent reports on solid lipid extrusion [5,9], is the high drug load of 80% and the very good water solubility of sodium benzoate.

3.4. Stability

It is well known that lipids can undergo changes during thermal treatment [26]. Therefore, all lipid pellet batches were stored under accelerated conditions at 32 °C for 4 weeks, which is 10 °C under the melting point of Witocan 42/44, present in all formulations. This was done to examine the influence of ageing and long-time storage. Changes in the release profiles were expected before and after ageing, as seen in Figs. 8 and 9. In Fig. 9, all batches are presented where the thermal treatment had an effect on the release kinetics. The release of these batches was slower over the first hour of dissolution, but still complete within less than 2 h and all batches still comply with the demanded release of 80% in 60 min. It is interesting to note that this effect was seen in all batches containing Precirol ATO 5, whereas batches with Witocan 42/44 or Witocan 42/44 and Compritol 888 ATO (see Fig. 9) were unchanged

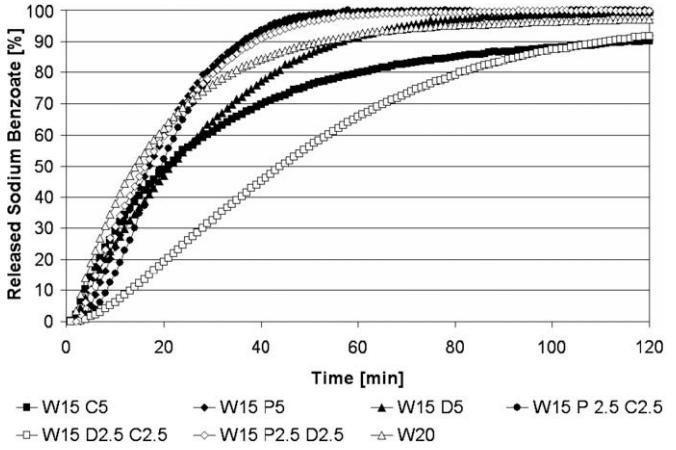

Fig. 7. Sodium benzoate release from lipid pellet formulations over time. Dissolution media: purified water (arithmetic mean, $n = 6$), temperature: 37 ± 0.5 °C, SD < 7%.

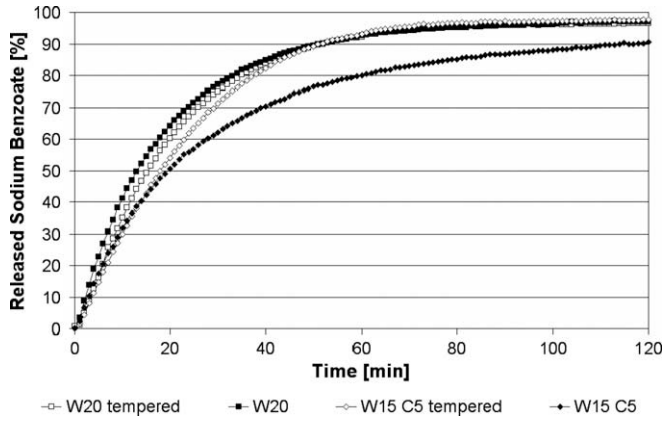

Fig. 9. Dissolution profiles of lipid sodium benzoate pellets before and after storage under accelerated conditions. Dissolution media: purified water (arithmetic mean, $n = 6$), temperature: 37 ± 0.5 °C, SD < 8%.

in their release behaviour. The composition of the lipids determines their tendency to undergo changes by thermal treatment. The reasons for the different behaviour of the lipid binders on the molecular scale are under investigation. It is essential in drug development that the drug dissolution profiles are kept constant. Therefore, it seems to be necessary to distinguish between the best shaped pellet formulation and the best maintenance of the drug release profiles.

4. Conclusion

The aim of this paper was to investigate whether lipids or combinations of different lipids are suitable pelletisation excipients for extrusion/spheronisation processes. In comparison to pellets with other binders, they have the advantages of low safety concerns or acceptable daily intake restrictions. We demonstrate in this study that it is possible to obtain such pellets through a cold solvent-free extrusion process, which is favourable for a number of reasons, e.g. suitability for thermal sensitive or hygroscopic drugs, no residual solvent burden, and simplicity to scale up. The production can be performed by extruders without temperature gradient control. Sodium benzoate pellets with a ternary combination of lipid binders show a drug release of >90% within 40 min in the dissolution studies. The influence of storage under elevated temperatures on dissolution profiles was detectable, as expected for lipid formulations, but is neglectable for most compositions. Complete drug release was delayed by up to 20 min with tempered pellets. Cold extrusion of lipids proved to be a valuable alternative to the conventional processes and binders resulting in spherical pellets with a high drug load, narrow size distribution and appropriate dissolution profiles.

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