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Research paper

Preparation of starch-based pellets by hot-melt extrusion

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ABSTRACT

Spherical starch pellets were directly and continuously produced using hot-melt extrusion and die-face pelletisation. In contrast to conventional pelletisation procedures, a discontinuous spheronisation step can be dropped. Pellets were produced based on four different starches (corn starch, pea starch, potato starch and waxy corn starch), four different active ingredients (ibuprofen, paracetamol, phenazon and tramadol-HCl) and various additives. The resulting pellets exhibit a large mechanical stability, low porosity and small surface area. Pellets with a very narrow particle size distribution and particle sizes even in the micron scale can be produced. The drug is either dispersed or dissolved in the starch melt. Drug loadings of up to 80% are achievable. The drug release rate is controlled by the particle size, the combination of starch, active ingredient and additives. The release mechanism is determined by the used starch and the additives. Under normal circumstances, the starch matrix remains intact during dissolution with the exception of waxy corn starch pellets. Pellets based on that starch completely erode. Mathematical modelling revealed that the drug release mechanism from corn starch, pea starch and potato starch pellets is complex and based on diffusion as well as relaxation of the matrix.

1. Introduction

Compared with other drug-delivery systems, such as a single-unit dosage form, pellets have several advantages. They

- can improve the bioavailability;
- are easier to administer;
- cause less irritations in the gastrointestinal tract;
- lower the risk of dose dumping; and
- provide for dose flexibility [1].

Therefore, pellets are perfectly suited for paediatrics, geriatrics and clinical trials. Pellets can be produced through different procedures. Layering techniques, where the drug is coated onto a nonpareil, direct pelletisation in a high shear mixer [2,3] or wet extrusion and subsequent spheronisation steps [4] are well established and widely used. For some time, hot-melt extrusion has been gaining increasing interest in the pharmaceutical field due to the fact that the bioavailability of poorly water soluble drugs can be increased by the incorporation into a polymeric melt. Furthermore, the potential to create controlled release devices by melt extrusion offers an excellent way to achieve a tailor-made drug release [5]. The obtained melt can be processed in various different ways, and one for option is pelletisation. Two major melt pelletisation techniques are typically used in the polymer industry: the strand granulation and the die-face pelletisation [6]. When using a strand granulator, the melt strand is drawn either via a conveyor belt or feed rolls of the granulator through a cooling medium, such as water or air to the cutting knives or breaking device of the granulator. The solidified polymer melt is then cut or broken into cylindrical pieces and spheronised discontinuous. In the conventional method of production, a later step may involve using a heated spheroniser (Fig. 1). The other widely applied melt pelletisation technique in the polymer industry is the so-called die-face pelletisation. The molten extrudate is cut at the die-face and transported to the next processing stage by, for example, vacuum (Fig. 2). Die-face pelletisation offers the opportunity to produce pellets without contact to a cooling medium and the risk of strand breakage during the cooling phase. The largest advantage of die-face pelletisation though is the fact that the granule swells to an almost spherical shape as a result of the viscoelasticity of the polymer melt. Further spheronising steps become unnecessary, and a continuous production of spherical pellets is possible. The spectrum of polymer melts that can be processed with die-face pelletisation is smaller compared with classical strand pelletisers. Low viscous and smeary polymer melts usually cannot be pelletised through this technique. However, if the material properties allow the appliance of die-face pelletisation, it should be preferred over other pelletising techniques because of its advantages. The main objective of this study was the development of a reproducible and continuous hot-melt extrusion and die-face pelletisation process that would lead to

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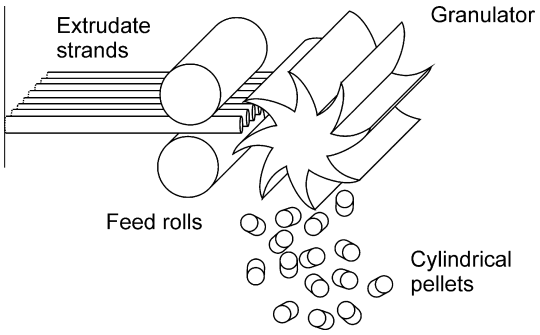

Fig. 1. Schematic representation of a strand granulator.

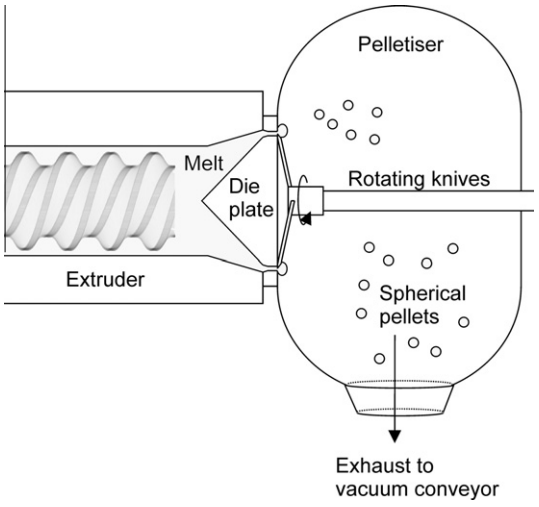

Fig. 2. Schematic representation of a die-face pelletiser.

spherical starch-based pellets with controllable drug release characteristics. The hot-melt extrusion of starches is a well-established process in the food technology industry; nevertheless, only few attempts have been made to use starch as a melt extruded polymer matrix for drug delivery [7–9]. This is quite surprising considering the fact that starch is widely used in the pharmaceutical industry due to its ubiquitous availability, its nontoxicity, low cost and broad range of derivatives that offer different functionalities. Starch melts usually can be processed by hot-melt extrusion at fairly low temperatures (<100 °C), which makes them suitable for even thermosensitive active ingredients. Four different starches were chosen as polymer matrix (corn starch, pea starch, potato starch and waxy corn starch). Four different active ingredients were selected as model drugs. Two highly aqueous soluble molecules: phenazon and tramadol-HCl (both BCS Class I) and two poor aqueous soluble drug: ibuprofen (BCS Class II) and paracetamol (BCS Class III) [10]. Different additives were used to modify the drug release. For a better understanding of the underlying drug release mechanisms, mathematical modelling of the obtained dissolution data was performed.

2. Materials and methods

2.1. Materials

Corn starch, pea starch, potato starch and waxy corn starch (Waxilys 200®) (Roquette Freres, Lestrem, France); ibuprofen (BASF, Ludwigshafen, Germany); paracetamol (Micron Technologies Ltd., Dartford, United Kingdom); phenazon (Fagron, Barsbüttel, Germany); tramadol hydrochloride (Mundipharma, Limburg, Germany); polyacrylate (Eudragit S100® and Eudragit L100®) and highly dispersed silicon dioxide (Aerosil 200®) (EVONIK, Darmstadt, Germany); microcrystalline cellulose (ProSolv SMCC 90® and Vivapur 12®) (JRS, Rosenberg, Germany); polyvinylpyrrolidone (Kollidon CL-F® and Kollidon 90®) and PVP-Vac-copolymer (Kollidon VA 64®) (BASF, Ludwigshafen, Germany); sodium hydrogen carbonate (Grüssing, Filsum, Germany). All chemicals have a reagent grade according to Ph. Eur.

2.2. Determination of melt flow properties

Apparent viscosities of the starch melts were measured using a Haake Minilab Rheomex CTW5 capillary rheometer (Thermo

Table 1
Extrusion parameters for the production of starch pellets; composition of the premix: 90% starch + 10% active ingredient (*m*|*m*).

Starch	Active ingredient	Formulation #	Dosing (kg/h)		Screw speed (rpm)	Temperature heating zone (°C)									
			Solid	Liquid		1	2	3	4	5	6	7	8	9	10
Pea starch	Without	1	1.8	0.4	250	20	50	50	80	80	80	80	80	80	90
	Ibuprofen	2	0.9	0.4	200	20	50	50	75	75	85	85	85	85	93
	Paracetamol	3	1.9	0.3	250	20	50	50	75	75	75	75	75	75	80
	Phenazon	4	1.9	0.3	250	20	50	50	80	80	80	80	80	80	90
	Tramadol-HCl	5	1.9	0.4	250	20	50	50	77	77	77	77	77	77	86
Potato starch	Without	6	0.96	0.22	250	20	50	50	62	62	62	62	62	62	69
	Ibuprofen	7	0.9	0.3	200	20	50	50	75	75	75	75	75	75	83
	Paracetamol	8	1.9	0.3	200	20	50	50	75	75	75	75	75	75	80
	Phenazon	9	1.9	0.3	250	20	50	50	80	80	80	80	80	80	90
	Tramadol-HCl	10	1.9	0.3	250	20	50	50	80	80	80	80	80	80	90
Corn starch	Without	11	1.8	0.4	250	20	50	50	80	80	80	80	80	80	90
	Ibuprofen	12	1.9	0.3	250	20	40	40	75	75	75	75	75	75	85
	Paracetamol	13	1.9	0.3	250	20	50	50	75	75	75	75	75	75	80
	Phenazon	14	1.8	0.4	250	20	50	50	75	75	75	75	75	75	80
	Tramadol-HCl	15	1.9	0.3	200	20	50	50	75	75	75	75	75	75	85
Waxy corn starch	Without	16	1.8	0.4	250	20	50	50	80	80	80	80	80	80	90
	Ibuprofen	17	1.08	0.32	100	20	50	50	75	75	75	75	75	75	83
	Paracetamol	18	1.9	0.3	250	20	50	50	80	80	80	80	80	80	90
	Phenazon	19	1.9	0.3	250	20	50	50	80	80	80	80	80	80	90
	Tramadol-HCl	20	1.9	0.3	200	20	50	50	75	75	75	75	75	75	80

Table 2
Extrusion parameters for the production of starch paracetamol pellets; composition of the premix: 90 − *X*% starch + 10% paracetamol + *X*% additive (*m*|*m*).

Additive		Dosing (kg/h)		Screw speed (rpm)	Temperature heating zone (°C)									
Amount in premix (% (*m*|*m*))		Solid	Liquid		1	2	3	4	5	6	7	8	9	10
Without	–	1.9	0.3	250	20	50	50	75	75	75	75	75	75	80
Aerosil 200	0.5	1.92	0.39	400	20	50	50	75	75	75	75	75	75	80
Eudragit L100	10	1.92	0.32	400	35	50	65	70	70	70	70	70	71	78
Kollidon CL-F	10	1.8	0.4	200	20	50	50	70	70	70	70	70	70	79
Kollidon VA64	10	1.92	0.12	400	35	50	65	95	95	90	90	85	85	91
Na-HCO_3	10	1.9	0.3	250	20	40	40	70	70	70	70	70	70	81
Povidon 90	10	1.92	0.18	400	36	50	65	95	95	90	90	85	85	88
ProSolv SMCC	10	1.9	0.3	200	20	50	50	70	70	70	70	70	70	78

Haake, Karlsruhe, Germany). The microcompounder was equipped with two conical counter rotating screws (diameter 5/14, length 109.5 mm) and a slit capillary (width 10 mm, height 1.5 mm, length 75 mm) with a pressure sensor at the in- and outlet of the capillary. Starch, water and active ingredient were mixed in a mortar. Six grams of the mixture were fed into the extruder manually. For all mixtures, the extrusion temperature was set to 90 °C. A screw speed ramp from 10 to 150 rpm was used. Each screw speed was held for 100 s, and the pressure build-up of the material in the capillary was measured ($n = 3$).

2.3. Preparation of pellets

Pellets were prepared by hot-melt extrusion and die-face pelletisation. The starches, active ingredients and additives were mixed for 10 min in a tumble blender. The resulting premix was filled into the gravimetric dosing unit (K-PH-CL-24-KT20, K-Tron, Switzerland) of a twin screw extruder (ZSE 18 HPPH 40D, Leistritz, Germany). The powder was dosed into the extruder, simultaneously mixed with water (Göhler Dosierstation, Göhler Anlagentechnik, Hösbach, Germany) and extruded using temperatures between the gelatinisation temperature of the used starch and 100 °C. The screw speed, the dosing of solid as well as liquid and the temperature profile of the extruder barrel had to be adapted for each mixture to the pressure build-up at the die plate, the appearance of the extrudates and the suitability of the melt for die-face pelletisation (and Table 2). The molten material was extruded through different die plates (Table 3). The strand was immediately pelletised using a die-face Micropelletizer (LM P18 PH, Leistritz, Germany). To obtain pellets with the same length, width and height, the cutting frequency of the pelletiser was adjusted using the following equation:

$$\mathrm{CF} = \frac{V_{Ex.}}{D_{Die}} \tag{1}$$

where CF is the cutting frequency in cuts per minute, $V_{Ex.}$ is the extrusion velocity (mm/min) and D_{Die} is the die diameter in (mm).

2.4. Laser diffraction measurements

The pellet size was determined by laser diffraction (volume distribution, diffractometer HELOS, Sympatec, Clausthal-Zellerfeld, Germany) ($n = 5$). The span value was calculated according to the following equation:

$$Span = \frac{X_{90}X_{10}}{X_{50}} \tag{2}$$

where X_{10}, X_{50} and X_{90} are the 10th, 50th and 90th percentile of the particle size distribution. The more the span value tends to zero, the smaller the particle size distribution. Particle size distributions with a span value $\leqslant 0.1$ can be regarded as monodisperse.

Table 3
Used die plates.

Die	Number of orifices	Orifice length (mm)	Orifice diameter (mm)
#1	12	2	0.5
#2	12	0.8	0.8
#3	8	2.5	1.0
#4	8	3	1.2

2.5. X-ray analysis

Wide-angle X-ray diffraction measurements were carried out on a Philips X'pert MPD Pro X-ray diffractometer equipped with a copper anode (Philips N.V., Eindhoven, Netherlands). A continuous scan from 5 to 35 °2θ with a step width of 0.017 °2θ and a step time of 29,845 s was performed.

2.6. Differential scanning calorimetry measurements

The solid state as well as the glass transition temperature of the extrudates was measured using a Pyris 1 differential scanning calorimeter (Perkin-Elmer, Überlingen, Germany); 5–7 mg of the whole pellets were weighted and sealed in a 50 µl alloy pan (Type: BO14-3019, Perkin-Elmer, Überlingen, Germany). The sample was cooled to −60 °C. The temperature was kept constant for 5 min. The sample was than heated to 250 °C with a heating rate of 50 K/min. By using the elevated heating rate, even small amorphous parts of the extrudates can be detected accurately [11–13]. Glass transition temperature was considered as $1/2\Delta c_p$ of the endothermal step in the DSC thermogram.

2.7. Tensile strength

The mechanical stability of the pellets was measured using a texture analyser TA.HDi (Stable Micro Systems Ltd., Godalming, United Kingdom) equipped with a 500 N (50 kg) measuring cell and a sensitivity of ±0.01 N (1 g). The punch diameter was 10 mm. Individual pellets ($n = 10$) were placed on the flat plate underneath the upper punch of the texture analyser. The probe moved downwards with a velocity of 0.5 mm/s. When a contact force of 0.5 N was registered, caused by the contact of the punch and the pellet surface, the punch stopped half way between the contact point and the flat plate's surface. The breaking force as well as the distance between the contact point and the stop point was registered. Spherical pellets tensile strength values were calculated according to the following equation:

$$\sigma = \frac{0.4 \times F_B}{\pi \times r^2} \tag{3}$$

where σ is the tensile strength, F_B is the breaking force and r is the covered distance of the punch from the pellet surface to the stop point, respectively, the radius of the pellet in crushing direction.

2.8. Specific surface area measurements

The specific surface area of the pellets was measured using the BET method (Nova 3000-Series BET, Quantachrome Corp., D-Odelzhausen; sample cell: special construction, for the pharmaceutical institute University of Bonn, D-Bonn). The samples were degassed in the sample cell for 24 h. The sample was automatically frozen in liquid nitrogen for 20 min. After 20 min, the device started to build up the requested pressures (adsorbate: dry Nitrogen, 5-point BET, P/P_0: 0.1, 0.15, 0.2, 0.25, and 0.3). When the desired pressure level was reached in the sample cell and remained constant (tolerance 0.05 mmHg) for at least four minutes, the pressure was increased to the next level. If the pressure could not be kept constant, the NOVA-BET automatically switched to the next pressure level after a maximum waiting period of 90 min. The measurements were accepted when the linear correlation (R^2) between the five points was larger than 0.995. Measurements were performed in duplicates. The results shown depict the arithmetic mean.

2.9. Porosity measurements

Relative density was calculated from the gas pycnometric density determined with a helium pycnometer (Ultrapycnometer 1000T, Quantachrome, Odelzhausen, Germany) and the apparent density measured with a mercury porosimeter (Pascal 140, Thermo Fisher Scientific Inc., Waltham, United States – Ma) according to the following equation:

$$RD = \frac{\rho_{Hg}}{\rho_{He}} \times 100 \quad (4)$$

where RD is the relative density, ρ_{Hg} is the apparent mercury density and ρ_{He} is the gas pycnometric density.

2.10. SEM photographs

Pellets were coated three times for two minutes under an argon atmosphere with gold (Polaron SC 7640 Sputter Coater, Quorum Technologies Ltd., East Grinstead, United Kingdom) and then observed with a scanning electron microscope (Hitachi S-2460N, Hitachi Ltd., Tokyo, Japan).

2.11. Drug release studies

In vitro drug release was determined using the USP XXIX paddle method at 50 rpm 900 ml dissolution medium at 37 °C (dissolution tester PTW S, Pharmatest, Hainburg, Germany).

As dissolution media were used: 0.1 N HCl ($n = 3$) and phosphate buffer, pH 6.8 ($n = 3$). Samples were withdrawn and replaced automatically (pump Ismatec Ecoline VC-MS/CA 8-6, used hoses Ismatec Tygon LFL, ID: 2.62 mm; AD: 4.8 mm, Wertheim-Mondfeld, Germany) at 0, 5, 10, 15, 20, 30, 45, 60, 90 and 120 min. If the drug was released slower, samples were analysed on an hourly basis from minute 120 to 420 and every other hour from minute 420 to 1440. The amount of released active ingredient was measured UV spectrophotometrically (UV-spectrophotometer: Perkin-Elmer Lambda 12, Überlingen, Germany): ibuprofen 226 nm, paracetamol 240 nm, phenazon 230 nm and tramadol-HCl 273 nm.

3. Results and discussion

3.1. Melt rheology

The flow properties of a polymer melt have a large influence on the extrusion process. They determine:

- the swell of the extrudate after it was pressed through the die [14],
- the probability that melt fracture occurs [15] and
- the pressure build up at the die and inside of the extruder [16].

Therefore, the die geometry, the screw speed and screw configuration and the possible material throughputs are all depending on the properties of the polymer melt.

According to the Hagen–Poiseuilles equation (Eq. (5)), the pressure drop (ΔP) in a Newtonian liquid flowing laminar and incompressible through a cylindrical capillary is proportional to the volume throughput (V), the dynamic viscosity (η) of the liquid as well as the length (l) and radius (r) of the capillary.

$$\Delta P = \dot{V} \times \eta \times \frac{8 \times l}{\pi \times r^4} \quad (5)$$

When using a slit capillary, Eq. (5) has to be adapted to the different geometry [17], which leads to the following equation:

$$\Delta P = \dot{V} \times \eta \times \frac{12 \times l}{h^3 \times w} \quad (6)$$

where h is the height and w the width of the slit capillary. The Haake Rheomex CTW5 capillary rheometer measures the pressure drop in the capillary. The volume throughput is given by the screw speed because of the fact that counter rotating screws with a high conveying efficiency of nearly 100% are used. Assuming laminar Newtonian flow of the melt through the capillary, the viscosity and the capillary wall shear rate value was calculated. Due to the fact that polymer melts are usually pseudoplastic liquids, these values are incorrect. Furthermore, the shear history of the material in dependence of the screw rotation can only be estimated. The calculated apparent values therefore can only be used for orientational purposes. Nevertheless, they offer an interesting insight into the behaviour of polymer melts. By comparing the pure starch melts without any active ingredients or additives (except for water), it becomes obvious that each starch has a different viscosity. Pea starch exhibits the highest and waxy corn starch the lowest apparent melt viscosity (Fig. 3). Exemplarily, the influence of the four different active ingredients on the apparent corn starch melt viscosity is shown (Fig. 4). It can be seen that the active ingredients act as expected as plasticisers and change the melt rheology. This highlights the fact that each mixture has its own unique flow properties and that the melt extrusion process has to be adjusted accordingly. Pea starch melts for example should be processed at higher temperatures, or more shearing elements should be used in the screw configuration to obtain the same melt viscosity as waxy corn starch melts.

3.2. Physicochemical properties of the pellets

From the above shown results, it is understandable why the dosing, screw speed and temperature profile vary for each blend (Tables 1 and 2). With the same extruder setting for all mixtures, it was not possible to obtain a melt, which was directly sliceable at the die face. After a correct extruder setup is empirically established, the production of pellets is feasible. The pellets differ in size and shape depending on:

- the die swell of the polymer melt;
- the cutting frequency of the pelletiser; and
- the used die plate.

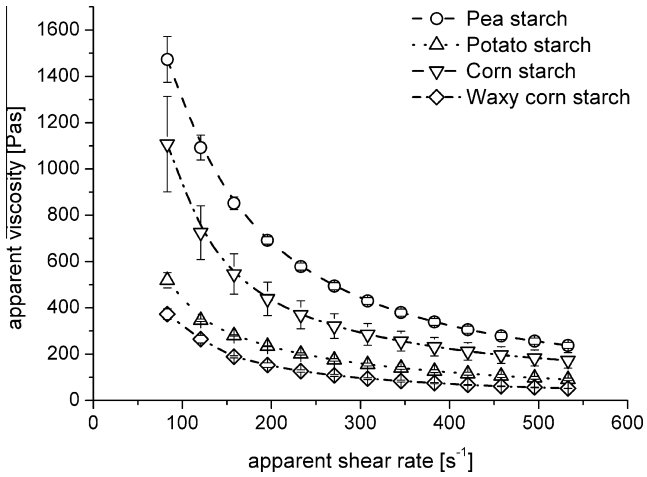

Fig. 3. Apparent viscosities of different starch melts at 90 °C; composition of the premix: 80% starch + 20% water ($m|m$).

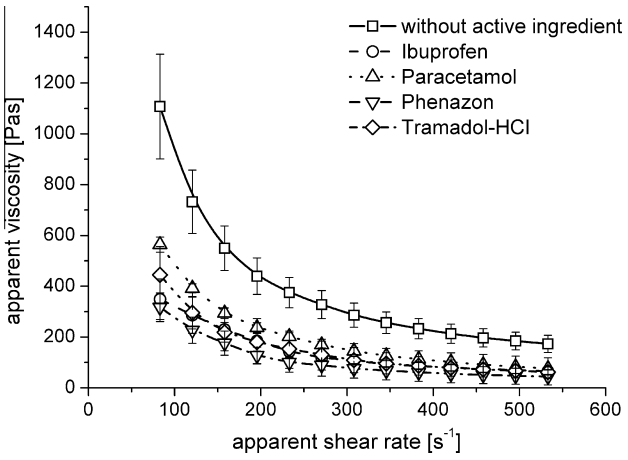

Fig. 4. Apparent viscosities of different corn starch active ingredient melts at 90 °C; composition of the premix without active ingredient: 80% starch + 20% water ($m|m$); with active ingredient: 70% starch + 13.3% active ingredient + 16.7% water.

The pellets usually become spherical because of the viscoelastic properties of the melt. If the die swell is not strongly pronounced, a more cylindrical shape is obtained (Fig. 5). In addition, if the cutting frequency is too high, more ellipsoid pellets are generated.

The particle size distribution of the produced pellets is very narrow. Span values of usually 0.5 or lower can be achieved (Table 4). The particle size is on the one hand determined by the used polymer. Potato starch melt exhibits a fairly strong die swell; therefore, potato starch pellets usually are bigger than pellets produced with other starches (Fig. 6). On the other hand, the particle size is also controllable by the used die plate. Exemplarily, the particle size distributions (q_3^*) of potato starch ibuprofen pellets extruded through different die plates are shown in Fig. 7. It can be seen that narrow particle size distributions even in the micron scale can be produced with hot-melt extrusion and die-face pelletisation of starch melts. The specific surface area of the pellets is generally small. This finding is consistent with the measured relative density, which is usually close to 100% (Table 5). This result is also in line with the scanning electron micrographs (Fig. 8). The surface of the pellets is usually smooth (A), but can exhibit irregularities on the surface (B) that could be caused by high pressure and shear force in the die. This could be an indication for beginning of melt flow instabilities. On closer inspection of the fracture face of the extrudates, only a few intraparticular pores can be seen. This is most likely a result from evaporating water during the hot-melt extrusion (C). X-ray diffractograms reveal that the active ingredients can be solved or dispersed in the starch matrix. The more lipophilic substances ibuprofen and paracetamol are usually dispersed, whereas the more hydrophilic substances phenazon and tramadol-HCl are dissolved. By comparing the blend before and after extrusion, it can be seen that the crystallinity peaks of the starch disappear but remain visible for the lipophilic substance (Fig. 9). This indicates that the lipophilic substance was dispersed in an amorphous starch matrix. After extruding the starch and

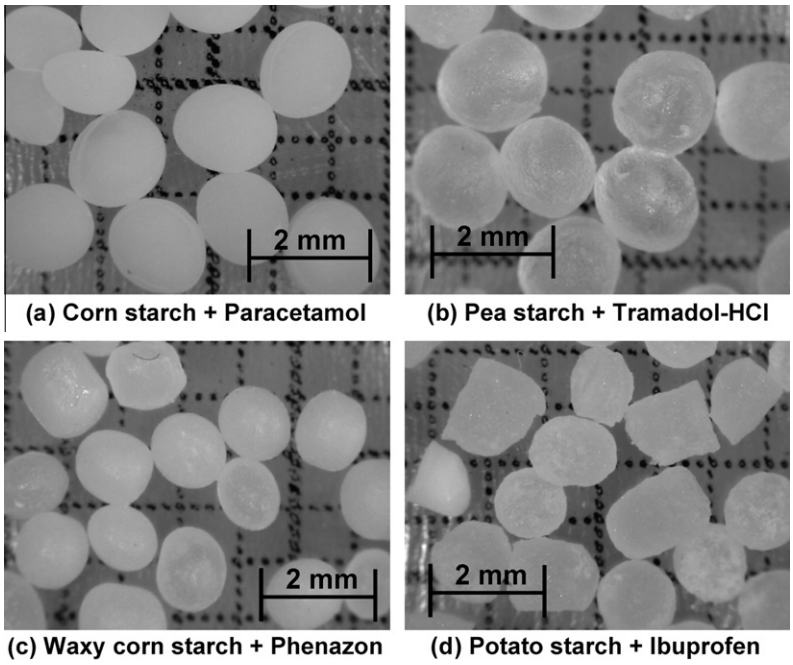

Fig. 5. Appearance of different starch active ingredient pellets; composition of the premix: 90% starch + 10% active ingredient ($m|m$).

Table 4
Span values of the particle size distributions of starch pellets produced according to Table 1; used die plate: 8 × 1.2 mm.

	Without	Ibuprofen	Paracetamol	Phenazon	Tramadol-HCl
Corn starch	0.49	0.47	0.59	0.43	0.42
Pea starch	0.46	0.41	0.83	0.54	0.41
Potato starch	0.39	0.39	0.57	0.71	0.38
Waxy corn starch	0.54	0.49	0.35	0.40	0.34

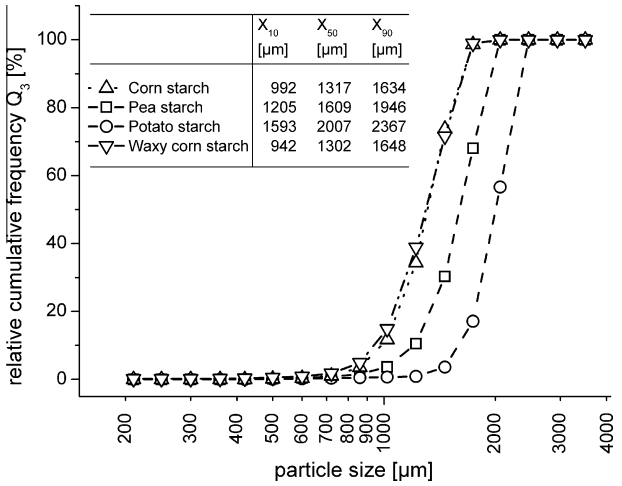

Fig. 6. Particle size distributions of different starch pellets without active ingredients; used die plate: 8 × 1.2 mm, relative cumulative frequency distribution (Q_3).

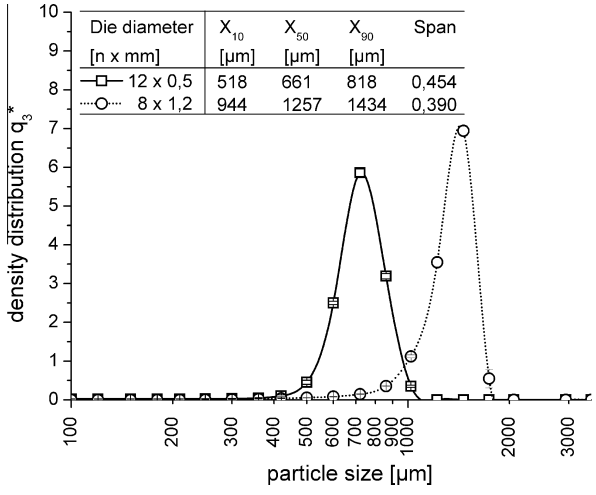

Fig. 7. Particle size distribution of potato starch ibuprofen pellets extruded through different die plates; used die plate: 12 × 0.5 mm and 8 × 1.2 mm; composition of the premix: 90% potato starch + 10% active ingredient (*m*|*m*), density distribution (q_3^*).

hydrophilic active ingredient mixture, only an amorphous halo can be detected (Fig. 10). This leads to the conclusion that a solid amorphous starch solution was formed during the extrusion. This conclusion is also supported by the DSC measurements. For the extrudates consisting of starch and hydrophilic active ingredient, only one amorphous phase could be detected. The combination of starch and lipophilic active ingredient led to more complicated DSC thermograms with several phase transition. In the case of extrudates containing paracetamol, at least two different amorphous phases and a crystalline phase could be detected. The formation of a solid solution of a highly water soluble drug in a starch matrix was not unexpected and has already been shown in previous works from Rein and Wauer [9]. Besides the particle size and the solid state, another important physicochemical property of pellets is their mechanical stability. Good mechanical stability of the pellets allows further processing steps like coating and filling into capsules. The mechanical strength of the extrudates is large (Table 7). The variations in the mechanical stability may have different reasons. Differences in the porosity could play a role here. Another influence could be that the melt solidified at a fast pace. Depending on the temperature, viscosity and relaxation time of the glassy melt stresses in the extrudate may or may not be relieved before the melt hardens. These tensions remain in the material until an outer force disequilibrates the metastable system and the tensions discharge abruptly. To evaluate the influence of the starch and/or the active ingredient on the mechanical stability of the matrix, a tempering of the extrudate should be conducted. The tensile strength is always larger than 4 MPa. A tensile strength value for pellets of 1 MPa can be regarded as sufficient for coating processes [18]. Therefore, melt extruded starch-based pellets seem to be suitable for coating processes or further processing not only because of their spherical shape and controllable size but also because of their sufficient mechanical strength.

Table 5
Specific surface area and relative density of starch pellets produced according to Table 1; Quantile of means (n = 20); used die plate: 8 × 1.2 mm.

	Minimum	Q1	Median	Q3	Maximum
Specific surface area (m^2/g)	0039	0168	0229	0402	1298
Relative density (%)	82	97	98	99	100

3.3. Drug release

One of the major objectives of this paper is the modification and the understanding of drug release from melt extruded starch-based pellets. The easiest way to modify the drug release is obviously a change in the particle size. In Fig. 11, the cumulative dissolution of paracetamol from corn starch pellets with different particle sizes is shown. The pellets were produced using all four die plates (Table 3) and the extruder setting for formulation #11. As can be seen, the drug release can be altered dramatically by the particle size. The duration until 85% (t_{85}) of the drug are released is tripled by doubling the median particle size (X_{50}). From the smallest particles with a mean diameter of 877 µm, 85% of the drug is released after 27 min compared with 73 min for particles with X_{50}: 1530 µm. Another possibility to control the drug release is the incorporation of different additives into the melt. Most of the tested additives did not alter the drug release from corn starch pellets (Fig. 12). Only Kollidon VA 64 and Aerosil 200 significantly influenced the drug release. The addition of Kollidon VA 64 leads to a fast disintegration of the pellets in the dissolution media and speeds up the drug release by a factor of 2–3. The addition of 0.2% (*m*|*m*) Aerosil 200 is slowing down the drug release. By adding sodium bicarbonate, effervescent pellets with a pH-depending release can be produced. The used starch also influences the drug release. Corn, pea and potato starch pellets remain intact in the dissolution medium, whereas waxy corn starch pellets completely erode. This leads to different drug release rates. In Fig. 13, the tramadol-HCl and ibuprofen release from waxy corn and pea starch pellets in phosphate buffer is exemplarily compared. The velocity of drug release from waxy corn starch pellets is independent of the incorporated active ingredient. This is not the case for pellets

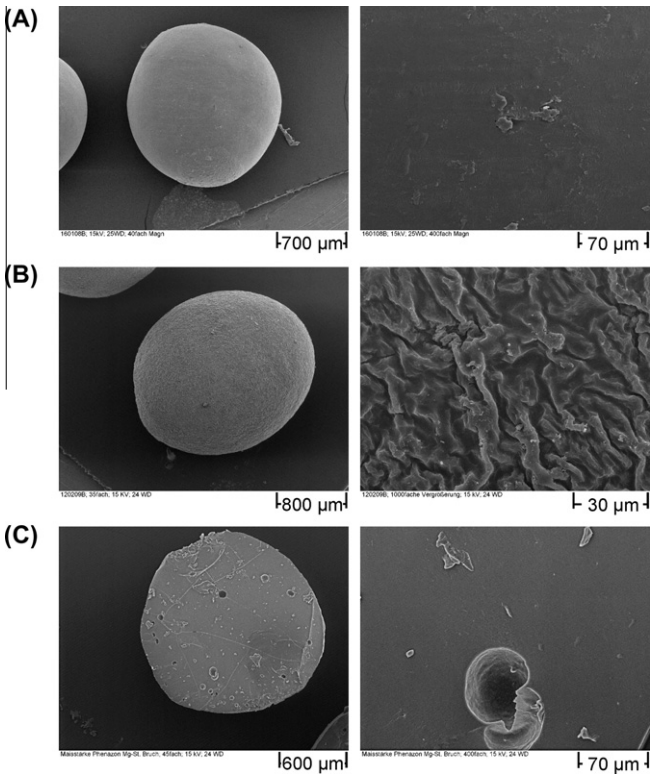

Fig. 8. Scanning electron micrographs of pellets based on (A) pea starch and paracetamol (formulation #3), (B) corn starch and paracetamol (formulation #13) and (C) corn starch and phenazon (formulation #14). (A and B) Top view on the intact surface, (C) top view on the fracture face.

Table 6
Glass transition temperature of the amorphous phase with the lowest glass transition temperature of 5–7 mg starch pellets produced according to Table 1 [°C]; arithmetic mean and standard deviation ($n = 3$) n.d.: no amorphous phase detectable; used die plate: 8 × 1.2 mm.

	Without	Ibuprofen	Paracetamol	Phenazon	Tramadol-HCl
Corn starch	70	n.d.	70*	67	73
Pea starch	67	62	69*	71	75
Potato Starch	81	78	70*	68	84
Waxy corn starch	66	62	73*	70	71

* Two detected glass transitions.

based on the other starches where the drug release is clearly influenced by the used active ingredient. Depending on their chemical properties and the molecular structure of the starch matrices, the diffusion coefficient of the active ingredient changes for each combination of starch and drug. Ibuprofen as a high lipophilic molecule possesses a smaller diffusion coefficient than tramadol-HCl in pea starch pellets leading to a slower drug release rate.

For a better understanding of the drug release mechanism, mathematical modelling of the cumulative drug release data was performed. Assuming sphericity of the pellets, the drug release data were fitted nonlinear from M_t/M_∞ 0–0.6 using Eq. (6) that was proposed by Peppas and Sahlin for matrices with a drug release mechanism that can be based on diffusion, relaxation or a combination of both [19]:

$$\frac{M_t}{M_\infty} = k_1 t^{0.43} + k_2 t^{0.85} \quad (6)$$

M_t/M_∞ is the cumulative amount of drug released at the time t, k_1 is the velocity constant of diffusion and k_2 the velocity constant of relaxation. The amount of drug that is released by diffusion also called diffusional fraction (F) can be calculated with:

$$F = \frac{1}{1 + \frac{k_2}{k_1} t^{0.43}} \quad (7)$$

The results for corn starch paracetamol pellets that were extruded with increasing amounts of paracetamol and the extruder settings from formulation #13 are shown in Table 8. The dissolution data can be described very well with the mathematical model. For the pellets with a low amount of paracetamol (10–20%), the coefficient of diffusion (k_1) is larger than the velocity coefficient of relaxation (k_2). This picture is inversed when the amount of drug in the matrix is increased. With the help of the two velocity coefficients, the diffusional fraction was calculated. As can be seen in Fig. 14, it was established that the drug release is a complex mixture of diffusion and relaxation phenomena. The curvature of the dissolution profiles can be explained well if the drug release mechanism is dominated by diffusion ($F > 0.6$) for the pellets with a lower amount (10–20%) of active ingredient. For pellets with higher amounts of paracetamol (50–80%), the drug release mechanism seems to shift towards a zero-order kinetic ($F < 0.2$) and is mainly influenced by the relaxation of the starch matrix and not the diffusion of paracetamol out of the pellet. Further investigations into the drug release mechanism as well as a simple mathematical model to describe the drug release from spherical starch pellets will be subject of another article. The stability of amorphous solid solutions is of significant interest. Recrystallisation of the amorphous drug and/or the amorphous matrix can alter the drug release rate of the dosage form. According to Hancock [20], an amorphous solid solution may be instable during storage if the glass transition temperature is not 50 °C or more above the storage temperature. For a solid amorphous dosage form that is stored at 20 °C, an optimal glass transition temperature would have to be at least 70 °C. The measured glass transition temperatures (Table 6) led to the assumption that the extrudates may not all be stable over longer storage periods. The extrudates were therefore stored at 25 °C and 65% rH for two years. No changes in the crystallinity were detected. The drug release rate changed during storage. In the worst case (corn starch paracetamol pellets) the time until 80% of the drug was released varied from 32 min (after production) to 43 min (2 years of storage). These results were surprising. Previous studies from Rein and Wauer could clearly show that amorphous extrudates based on different starches and tramadol-HCl remained stable during 2 years of storage [9].

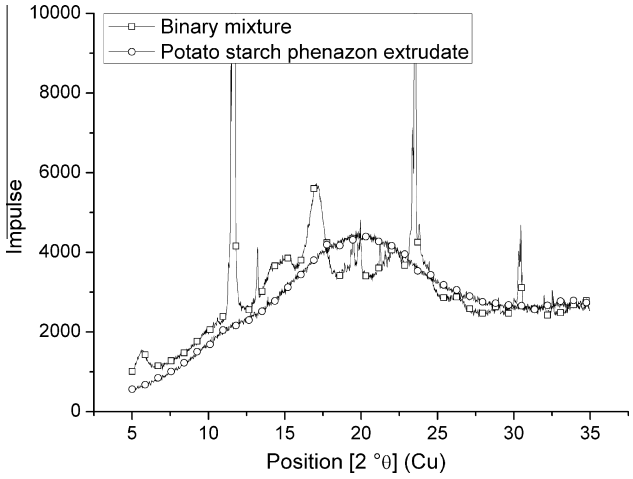

Fig. 9. X-ray diffraction pattern of potato starch phenazon blend before and after extrusion; formulation #9.

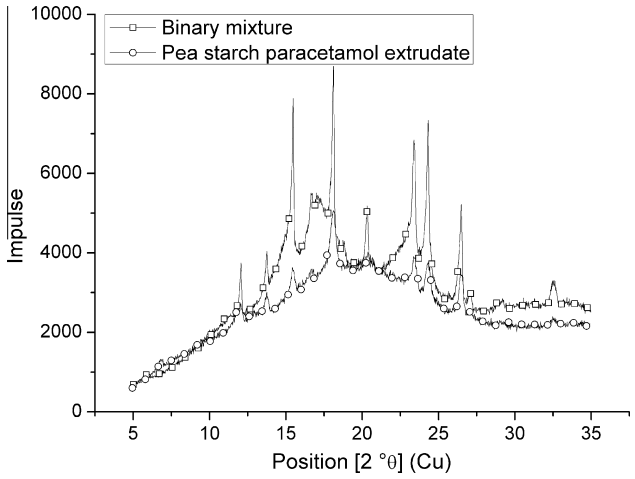

Fig. 10. X-ray diffraction pattern of pea starch paracetamol blend before and after extrusion; formulation #3.

Table 7
Tensile strength values ± standard deviation [MPa] of starch pellets produced according to Table 1; used die plate: 8 × 1.2 mm.

	Without	Ibuprofen	Paracetamol	Phenazon	Tramadol-HCl
Corn starch	38 ± 8	9 ± 2	35 ± 4	9 ± 1	22 ± 6
Pea starch	18 ± 10	16 ± 4	32 ± 5	18 ± 10	13 ± 3
Potato starch	9 ± 6	12 ± 4	25 ± 8	7 ± 5	4 ± 3
Waxy corn starch	10 ± 5	10 ± 5	11 ± 1	5 ± 1	10 ± 5

4. Conclusions

Hot-melt extrusion and die-face pelletisation of starch melts is an interesting approach to continuously produce spherical pellets with a very narrow particle size distribution. The particle shape and size is determined by the die swell of the melt and is controllable by the used die plate. Pellets with particle sizes from 500 μm to 2 mm can be produced. A broad range of active ingredients with a variety of chemical properties can be incorporated into the starch melt. The resulting solid dosage form is either a solid solution or solid dispersion with low porosity, small surface area and large mechanical stability. The large mechanical stability makes them suitable for further processing like coating or filling into capsules. Mixtures with drug loadings of up to 80% can be extruded. The rate of drug release is controllable by the particle size and the used mixture. A pH-dependent drug release can be achieved with effervescent sodium bicarbonate containing pellets. The mechanism of

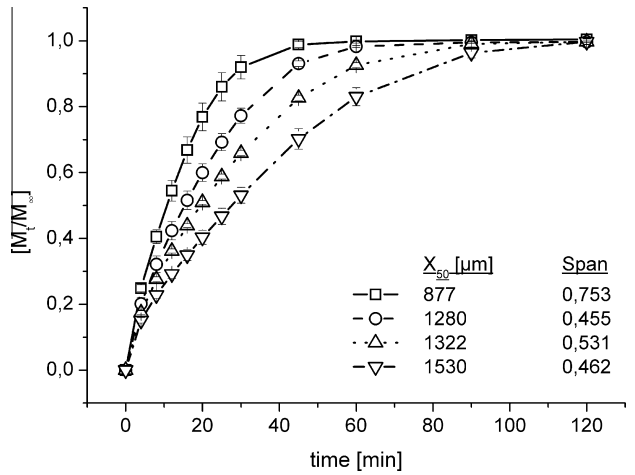

Fig. 11. Cumulative paracetamol release from corn starch pellets extruded through different die plates; used extrusion profile: formulation #11.

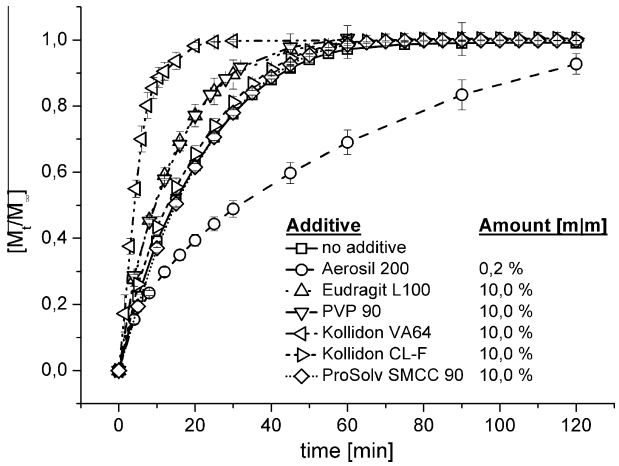

Fig. 12. Cumulative paracetamol release from corn starch pellets; drug release in phosphate buffer ($n = 3$); extrusion parameters and composition of the premix see Table 2.

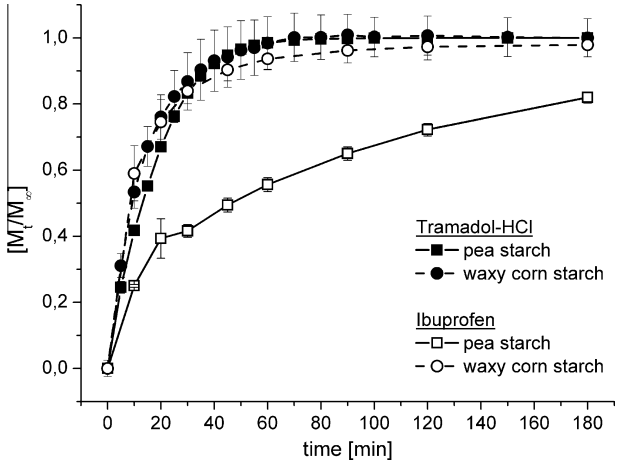

Fig. 13. Ibuprofen and tramadol-HCl release from pea starch and waxy corn starch pellets in phosphate buffer, pH 6.8; formulations #2, 5, 17, 20.

Table 8
Parameters of the nonlinear fit (Eq. (6)) of the drug release from corn starch paracetamol pellets with increasing amounts of paracetamol; composition of the premix: 99.8 − *X*% corn starch + 0.2% Aerosil 200 + X% paracetamol; extruder settings: formulation #13; k_1: velocity constant of diffusion [$min^{-0.43}$]; k_2: velocity constant of relaxation [$min^{-0.85}$].

Paracetamol (%)	k_1	k_2	R^2_{corr}
10	0.0650	0.0127	0.999
20	0.0514	0.0072	0.999
30	0.0342	0.0134	1.000
40	0.0238	0.0101	1.000
50	0.0147	0.0314	0.999
60	0.0197	0.0283	0.998
70	0.0073	0.0282	0.999
80	0.0309	0.0393	0.997

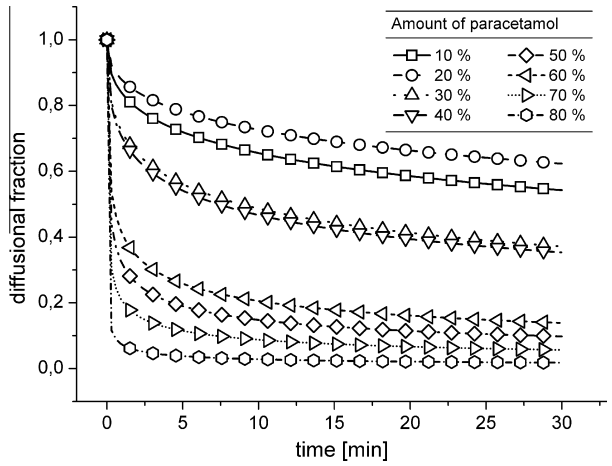

Fig. 14. Theoretical diffusional fraction of drug release for corn starch paracetamol pellets extruded with increasing amounts of paracetamol ($m|m$); composition of the premix: 99.8 − *X*% corn starch + 0.2% Aerosil 200 + X% paracetamol; extruder settings: formulation #13.

drug release for waxy corn starch pellets is erosion based and independent of the chemical properties of the active ingredient. For corn, pea and potato starch pellets, the release mechanism is a complex mixture of diffusion and relaxation phenomena.

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