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RESEARCH ARTICLE

Use of the Direct Compression Aid Ludiflash® for the preparation of pellets via wet extrusion/spheronization

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Abstract

Objective: Conventional solid oral dosage forms are unsuitable for children due to problems associated with swallowing and unpleasant taste. Additionally, the limit of tablets lays in the patient adapted dosing. Therefore, the suitability of Ludiflash®, a direct compression aid for orally disintegrating tablets, was investigated for the preparation of individually dosable pellets.

Materials and methods: Micropellets consisting of Ludiflash® and small amounts of microcrystalline cellulose were prepared via the wet extrusion/spheronization technique. Paracetamol and ibuprofen were applied as model drugs. The obtained pellets were characterized with respect to drug release and disintegration characteristics, mechanical properties, as well as size and shape.

Results and discussion: Drug loading was possible up to 30% for ibuprofen and even up to 50% for paracetamol. Higher ibuprofen loadings resulted in considerably slowed drug release and higher paracetamol contents yielded in non-spherical pellets. *In vitro* release studies revealed that more than 80% of the drug was released within 30 and 60 min for paracetamol and ibuprofen, respectively. Drug release rates were highly influenced by the pellet disintegration behavior. Investigations of the release mechanism using the Korsemeyer-Peppas approach suggested Super Case II drug transport for all paracetamol formulations and anomalous drug transport for most ibuprofen formulations. All pellets exhibited a low porosity and friability, as well as a sufficiently high tensile strength, which was significantly influenced by the type of model drug.

Conclusion: Ludiflash® can be applied as main excipient for the preparation of individually dosable pellets combining fast drug release and a high mechanical stability.

Keywords: Fast drug release, multi-particulate dosage forms, disintegration, paracetamol, ibuprofen

Introduction

Most solid oral dosage forms, such as tablets and capsules, are unsuitable for children, due to problems associated with (i) swallowing, (ii) unpleasant taste and mouthfeel and (iii) correct dosing. As a consequence, the availability of solid drug formulations for the use in children is poor. Most of the medicines available include liquid systems, such as oral suspensions and oral solutions. A novel application of administration already available on the market is the *dose-sipping technology* (e.g. Clarosip®): pellets containing a single dose are placed in a drinking straw and swallowed, while drinking through this straw from any kind of beverage. However, the unpleasant taste of dissolved or suspended drugs often requires the use of artificial sweeteners. Therefore, the development of solid oral formulation-technologies has gained much attention. Multi-particulate dosage forms, composed of pellets or granules, offer a promising alternative.

Pellets are defined as *small, free flowing, spherical or semispherical units made up of fine powders or*

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granules of bulk drugs and excipients[1]. Typically, pellets for pharmaceutical applications have a diameter between 0.5 and 1.5 mm[2] and are required to fulfill a set of desired properties of pediatric dosage forms. They provide the possibility of individual dosing (according to body weight or body surface area), taste masking and facilitated administration, therefore, improving patient compliance. From the technological point of view, pellets show limited attrition, high mechanical stability, as well as the opportunity to tailor the dissolution behavior of the final dosage form. An established method for the preparation of pellets is the wet extrusion/spheronization process. Its advantage, compared to other granulation techniques, is the possibility to achieve high drug loadings without producing excessively large pellets[1]. Currently, microcrystalline cellulose (MCC) is the most commonly used extrusion and spheronization aid due to its ability to form a wet mass with proper rheological characteristics for subsequent extrusion/spheronization and to control water movement[3]. Typically, MCC pellets show prolonged drug release. Therefore, several attempts have been made to (partially) replace MCC by other excipients. Drug release from pellets was accelerated by using excipients, such as powdered cellulose[4], chitosan[5,6], starch[7], alginate[8], κ-carrageenan[9–12] and pectinic acid[13,14] instead of pure MCC. From the above-mentioned extrusion excipients, only pellets containing high drug loadings combined with starch[7], chitosan[5], κ-carrageenan[9,10,15] and pectinic acid[13,14] are reported to release the drug immediately in test medium due to fast disintegration and dissolving.

The aim of the present study was the development of pharmaceutical pellets via the wet extrusion/spheronization technology using Ludiflash® as main excipient. Ludiflash® is a co-processed excipient that is intended for the preparation of orally disintegrating tablets and mini-tablets by direct compression. Typically, Ludiflash® tablets combine a high mechanical stability, a good mouthfeel and immediate drug release due to fast disintegration abilities. The limit of tablets, however, is the patient adapted dosing. Therefore, the suitability of Ludiflash® for the preparation of individually dosable pellets, by the extrusion spheronization process, was investigated. Additionally, it was evaluated whether the beneficial properties of Ludiflash® are maintained when processed into pellets. Ludiflash® is composed of 90% D-mannitol, 5% Kollidon® CL-SF and 5% of Kollicoat® SR 30D. Mannitol acts as a filler and Kollidon® CL-SF is the actual disintegrant whose disintegrating ability is enhanced by Kollicoat®, a hydrophobic binder. Different water/ethanol mixtures were used as granulation liquid, because pure water is unsuitable for the applied process due to the high water solubility of mannitol. The water solubility of the active pharmaceutical ingredient (API) plays an important role in the final pellet properties[16,17]. Thus, two different model drugs showing high and low water solubility were used: paracetamol (water solubility 14.3 g/l) and ibuprofen (sparingly water soluble).

Methods and materials

Materials

Ludiflash® (volume median particle size 108.9 µm) was provided by BASF, Ludwigshafen, Germany. Paracetamol (volume median particle size 139.2 µm) and ibuprofen (volume median particle size 255.9 µm) were provided by G.L. Pharma, Lannach, Austria. Avicel® PH 101 (volume median particle size 77.11 µm) was purchased from Werba-Chem GmbH, Vienna, Austria. All materials were pharmaceutical grade and fulfilled the requirements of the European Pharmacopoeia (Pharm. Eu.). They were used as received. The particle sizes were determined via image analysis (Morphologi G3S, Malvern Instruments Ltd., Malvern, United Kingdom). Ethanol (Merck, Darmstadt, Germany) and mixtures of ethanol/purified water were used as binding liquids. For *in vitro* release characterization, 0.1 N hydrochloric acid (Merck, Darmstadt, Germany) and tris-phosphate-dodecahydrate buffer (Merck, Darmstadt, Germany) were used to simulate gastric and intestinal conditions. For the high-performance liquid chromatography (HPLC) analysis, triethylamine (Merck, Darmstadt, Germany) and acetonitrile (Merck KGaA, Darmstadt, Germany) were used as mobile phase. Ketoprofen (Sigma Aldrich Chemie GmbH, Munich, Germany) was applied as internal standard.

Methods

Pre-formulation of drug-free pellets

Since Ludiflash® alone does not exhibit sufficient plasticity for the extrusion/spheronization process (data not shown), formulations containing Ludiflash® and Avicel® PH 101 at a mass ratio of 9 to 1 were dry-blended in a closed high-shear mixer (Stephan UMC 5 electronics, Sympak Inc, Mundelein, IL). Hundred grams of the powder mixtures were wetted in an open planetary mixer (Kenwood Chef, Kenwood, Hampshire, Great Britain) with several granulation liquids (i.e. 95, 50, 40, 30 and 20% ethanol). The granulation fluid was added manually over a time period of 7 min. During wetting, the materials were scraped from the mixing bowl walls to ensure equal distribution of the liquid. The amount of granulation liquid was chosen such that moisture content of the wet powder mass was suitable for the extrusion process. For moisture determination of the wet powder mass, a halogen moisture analyzer (HR 73 Halogen Moisture Analyzer, Mettler Toledo International, Inc., Columbus, OH) was used. The wet mass was subsequently transferred into an axial single-screw extruder (Extruder Pharmex T35, Gabler Maschinenbau GmbH, Lübeck, Germany) and extruded through a 1-mm multi-hole die plate (2 mm in length, 895 holes). The screw with a diameter of 60 mm maximum and 40 mm minimum was driven at a constant speed of 80 rpm. The extrudates (60 g) were immediately transferred into a spheronizer (Sphaeromat 250 T,

Gabler Maschinenbau GmbH, Lübeck, Germany) with a cross-hatched friction plate of 250 mm diameter and were spheronized for 30 s at 610 rpm. All experiments were carried out at ambient temperature (i.e. between 22 and 25°C), and no external cooling was required. The obtained drug-free pellets were finally spread on stainless steel trays and dried in an oven (Heraeus Type 042 E, Heraeus, Hanau, Germany) for 17 to 18 h at 30°C, except those produced with 95% ethanol, which dried due to solvent evaporation at room temperature. Additionally, 0.5 g of Ludiflash® and Avicel® were compacted into disks and the contact angles of water and ethanol were evaluated using an EasyDrop System (Krüss, Hamburg, Germany) equipped with a CCD camera.

Preparation of drug-loaded pellets

Based on the results of the pre-formulation study, a Ludiflash®/Avicel® PH 101 mixture of 9:1 wetted with 30 and 40% ethanol was used for further investigations. In a first set of experiments, the excipients were mixed with paracetamol (20, 30, 40 and 50%) and wetted with 30% and 40% ethanol (Kenwood Chef, wetting time: 7 min). The extrusion process was carried out in the same devices with the same parameters as for the drug-free pellets; spheronization times ranged between 30 and 90 s at 610 rpm to achieve spherical pellets. The obtained pellets were finally tray-dried in an oven for 17–18 h at 30°C to constant weight. The moisture content of the wet mass and the pellets after spheronization and after drying was measured with the halogen moisture analyzer. In a second set of experiments, ibuprofen (20, 30, 40 and 50%) was used as model drug. The pellet preparation was performed in the same manner as for the paracetamol pellets. The contact angle of pure water and ethanol on the used APIs was measured following the same procedure as for the excipients.

Pellet characterization

Pellet size and shape. Each batch was sieved according to Pharm. Eu. 6.0 (2.9.3) to define the yield fraction (i.e. the desired product fraction between 0.8 and 1.25 mm). The samples were sieved with six analytical DIN sieves of 355–1250 µm aperture at an agitation of 50 vib/min until the endpoint was reached. A representative sample of more than 500 individual pellets was obtained for subsequent image analysis by using a rotary cone sample divider. Pellets were placed on a dark background, illuminated from above with a conventional desk light and mechanically separated. The image analysis was carried out using a digital camera (Canon EOS D30, Canon, Tokyo, Japan) and sophisticated image processing software (ImageJ, National Institue of Health, Bethesda, USA and Matlab, The MathWorks, Inc., Natick, USA). The Ferret's diameter and the aspect ratio (AR) were determined.

Pellet morphology. The surface and the cross-sectional surface of the pellets (drug-loaded and drug-free) were analyzed by scanning electron microscopy (SEM). For this analysis, pellets were cut mechanically with the help of a scalpel. The pellets and the cut pellets were mounted on stubs using a double-sided sticky band, sputter coated with chromium and examined in a scanning electron microscope (Zeiss Ultra 55, Carl Zeiss NTS GmbH, Oberkochen, Germany).

Pellet disintegration. Pellet disintegration was evaluated in de-ionized water using a tablet disintegration tester (Erweka Apparatebau GmbH, Hausenstamm Kr. Offenbach/Main, Germany) according to Pharm. Eu. 6.0 (2.9.1). Special open-ended transparent glass tubes with a diameter of 21.5 mm and a length of 77.5 ± 2.5 mm were used. Sieves (400 µm mesh size) were placed on the bottom of the tubes. Each tube was filled with 1 g of pellets, and cylindrical disks were placed on the top of the tubes to avoid floatation of the pellets. For each formulation, the disintegration time of six samples was determined at a speed of 30 dips per minute at 37.5 ± 0.5°C. Each test was performed over a time period of 10 min.

In vitro drug release characteristics. The release of paracetamol and ibuprofen from the different formulations was investigated *in vitro* according to USP 28. The rotating basket apparatus (Pharma Test Type PTWS III C, Pharma Test Apparatebau AG, Hainburg, Germany) was operated at a temperature of 37 ± 0.5°C and a stirring speed of 60 rpm. The *in vitro* dissolution characteristics of each formulation were determined six times.

For each dissolution test of paracetamol formulations, six vessels were filled with 750 ml 0.1 N hydrochloric acid to simulate gastric conditions. Pellet sample weights were adapted to a paracetamol amount of 1 g, representing the maximum partial dose. Paracetamol is soluble in acidic media, and thus, dissolution was expected to be completed within 2 h in hydrochloric acid. Samples of 1 ml were withdrawn from the dissolution media after 2, 4, 6, 8, 10, 20, 30, 40, 50, 60 and 120 min.

For each ibuprofen formulation, six vessels were filled with 0.1 N hydrochloric acid (750 ml each). The amount of pellets transferred into the baskets was adjusted to the mean common partial dose of ibuprofen, i.e. 0.3 g. After 2 h, 250 ml tris-phosphate-dodecahydrate buffer were added to switch the pH from 1.2 to 6.8, thereby simulating intestinal conditions. Due to the pH-dependent solubility of ibuprofen (i.e. insolubility in acidic media) dissolution was expected to start after the pH was increased. Samples of 1 ml were taken after 120 min (before the pH was switched), and then after 130, 140, 150, 160, 170, 180, 210 and 240 min.

The amounts of APIs released were quantified by reversed-phase HPLC (RP-HPLC; see HPLC analysis section). To investigate the *in vitro* release characteristics, the data from the HPLC analysis were plotted against time. Following the prescription of paracetamol (acetaminophen) and ibuprofen tablets in the USP, at least 80% of the API are demanded to be released within 30, respectively 60 min.

HPLC analysis. The drug concentration was determined adapting a method for the simultaneous detection of ibuprofen and paracetamol, developed by Ravisankar et al.[18]. A Merck system (Merck Hitachi, Merck Serono Co., Ltd., Tokyo, Japan) with a UV/VIS detector (215 nm, response time 0.5 s), a pre-column (Hypersil MOS 250 × 2.0 mm, particle size 5 µm, Merck Serono Co., Ltd., Tokyo, Japan) and an analytical column (Hypersil MOS 250 × 4.0 mm with a particle size of 5 µm, Merck Serono Co., Ltd., Tokyo, Japan) were used at ambient temperature. The mobile phase consisted of 0.2% triethyl amine (pH 3.4) in 50% acetonitrile. Ten microliters of the paracetamol samples were diluted with 890 µl mobile phase, and 20 µl of the ibuprofen samples were diluted with 880 µl mobile phase prior to injection. Hundred microliters of the internal standard solution (100 µg ketoprofen/ml mobile phase) were added to each sample. The injection volume was set to 20 µl, and the flow rate was 1.2 ml/min.

Mechanism of drug release. Different mathematical models were applied to describe the kinetics of the drug release from the micropellets. Selected portions of the obtained dissolution data were fitted according to (i) zero order kinetics (Equation 1), (ii) first order kinetics (Equation 2), (ii) the Weibull model (Equation 3) as well as to (iii) the Korsmeyer-Peppas model (Equation 4). SigmaPlot version 11 (SysStat) was used for data fitting.

$$A_t^* = A_0^* + k_0 t \tag{1}$$

where A_t^* is the fraction of drug dissolved at time t, A_0^* is the fraction of the drug dissolved at time zero and k_0 is the zero order release constant. A_t^* is defined as the ratio of the cumulative absolute amount of API dissolved at time t (A_t) and the amount of API dissolved at infinite time (A_∞). A_∞ should equal the amount of drug in the pellets at $t = 0$.

$$\ln A_t^* = \ln A_0^* + k_1 t \tag{2}$$

where k_1 is the first order release constant.

$$A_t^* = 1 - \exp\left(-\frac{t}{\tau}\right)^{\beta} \tag{3}$$

where τ is the time at which 63.2% of the API is dissolved and β is the Weibull shape factor.

$$A_t^* = Kt^n \tag{4}$$

where K is a constant incorporating structural and geometric characteristics of the dosage form n is the release exponent which is indicative for the release mechanism. An n value of 0.43 indicates Fickian release (diffusion-controlled release) for drug release from spheres. In the case of Case II transport (swelling controlled release from polymer matrices), n is 0.85. Values between these limits display anomalous transport (superposition of both phenomena). Occasionally, n values exceeding 0.83 are observed and are typically considered to be Super Case II transport kinetics. For determination of the release exponent, only portions of the dissolution profiles where $A_t^* \leq 0.6$ were used.

Pellet friability. The friability of the pellets was evaluated according to Pharm. Eu. 6.0 (2.9.41). Ten grams of the yield fraction of each pellet formulation were transferred into a friability tester for granules (Friabimat SA-400, Copley, Therwil, Switzerland). The sample was shaken for 240 s at the highest oscillation frequency (i.e. 400 min^{-1}) and subsequently sieved through a 355-µm sieve. Experiments were performed in triplicate. The pellets were required to show a weight loss below 1%.

Tensile strength. The mechanical characteristics were investigated using a rheometer (Physica MCR 301, Anton Paar GmbH, Graz, Austria) with a parallel plate measuring system (PP 25) used in the normal force mode without rotation. Each pellet was transferred into the system separately. Pellets were chosen randomly from a sample of the defined yield fraction (not more than 1 g) obtained by the rotary cone divider. The upper plate was moved down with a constant velocity of 0.5 µm/s. The fracture was defined as maximum force (F) during irreversible plastic deformation upon fracture. The tensile strength (σ) was calculated according to the following equation[19]:

$$\sigma = \frac{1.6F}{\pi d^2} \tag{5}$$

where d is the diameter of the pellet represented by the gap distance at the beginning of plastic deformation. Statistical tests (t-test or rank sum test if the populations were non-normal) were carried out in order to evaluate the impact of the type of API on the pellet strength dependent on the granulation liquid. Furthermore, the influence of the granulation liquid was investigated. P values below 0.050 indicated statistically significant differences.

Pycnometric density and mercury porosimeter density. Pycnometric density measurements of the pellets were performed using a helium-pycnometer Quantachrome Ultrapycnometer-1000 T (Quantachrome GmbH & Co. KG, Odelzhausen, Germany) at 25°C. The pellets were placed into a sample chamber with a volume of 20 cm^3 and were subsequently flushed with helium. The gas expanded, and the final pressure at equilibrium was recorded. Finally the density was calculated.

Mercury porosimetry was used to measure the pellet density utilizing a Quantachrome Poremaster 60-GT (Quantachrome GmbH & Co. KG, Odelzhausen, Germany). In order to conduct the measurements, the pellets (sample weight between 3.9 g and 5 g) were transferred into a sample chamber, which was then evacuated and finally filled with mercury according to the manufactures instructions. Experiments were conducted at 20°C. By using both methods, detailed information about the pellet porosity can be obtained.

Results and discussion

Pre-formulation and characterization of drug-free pellets

As described above, small amounts of MCC were added to ensure proper rheological characteristics of the wet mass for subsequent extrusion and spheronization. Powders of pure Ludiflash® and Avicel® PH 101 at a mass ratio of 9:1 were extruded using water/ethanol as granulation liquids. Since it is reported in literature that the ethanol content in the granulation fluid impacts the mechanical characteristics of pure MCC pellets[20–23], different ethanol concentrations ranging from 20 to 95% were applied. The amounts of granulation fluid used and the corresponding moisture contents of the wet masses are listed in Table 1.

During the process, several effects were expected to occur. During the wetting step, materials were wetted in case of hydrophilic interactions with the granulation liquid. From the contact angle measurements, it was found that all contact angles (i.e. water and ethanol on Ludiflash® and Avicel®) were below 90°, indicating that all powders were wetted by the granulation fluid. Ludiflash® partly dissolved in the aqueous component of the granulation liquid due to its high proportion of D-mannitol. Both Kollidon® CL-SF (i.e. crospovidone) and Avicel® PH 101 swelled due to the presence of water. During the extrusion step, the wet mass was kneaded, mixed and compacted due to the action of the screw and the high pressure built up in the die zone. Thus, capillary granulation liquid was likely to be squeezed from the wet mass due to the high pressure and acted as a lubricant[24]. When the wet mass was forced through the die, strands were formed, which broke after becoming too long. During spheronization, the strands were broken into (almost) equally-sized rods on the friction plate. Rods, accelerated due to centrifugal forces, impacted on the spheronizer wall and collided with each other multiple times, leading to a spheronization of the pellets. During drying, the granulation liquid was transported toward the outer surface of the pellets and evaporated. Dissolved components were likely to be transported toward the outer surface of the pellets. In a recent study, it was shown that dissolved components were transported back due to high concentration gradients[25]. In our case, however, more probably recrystallization of dissolved components occurred close to the pellet surface, and consequently, the concentration gradient disappeared. Due to recrystallization, solid bridge formation between primary particles might have occurred (mainly close to the surface of the pellets). MCC and Kollidon® CL-SF, the swelling compounds, are able to shrink during drying. On the one hand, shrinkage of specific compounds might lead to the formation of pores and a weakening of the pellets. On the other hand, it might result in the shrinkage of the whole pellet, thus reducing the pore space. However, it was shown before that total shrinking is more pronounced for pellets with a high content of swellable compounds[26].

Table 1. Formulation parameters for drug-free pellets.

Ethanol content (%(w/w))	Amount of granulation liquid used (g)	Moisture content of the wet mass (%)
20	32	25.15
30	33	23.27
40	35	24.98
50	33	22.70
95	23	18.10

In the experiments using 20–50% ethanol, the wet mass was first extruded at a screw speed of 80 rpm through a 1-mm die plate and spheronized at 610 rpm for 30 s. However, for the powders wetted with 95% ethanol, the screw of the extruder got stuck, as MCC only swells in water but does not swell in ethanol. It can be assumed that in this case extensive liquid movement during extrusion occurred due to the limited ability of MCC to hold the granulation liquid. This resulted in a dry mass that could not be extruded. Thus, ethanol concentrations of 95% were not further investigated.

The pellet size distributions obtained by sieve analysis demonstrated that all of the investigated formulations showed a yield between 61.9 and 74.8% in the desired size fraction (i.e. 0.8–1.25 mm in diameter). No clear trend of the pellet size distribution as a function of the ethanol content could be observed.

The disintegration studies, however, demonstrated that all formulations, except for the formulation prepared with 50% ethanol, showed disintegration times below 10 min. This was surprising, since it is described in literature that disintegration times of MCC-based pellets decrease with increasing alcoholic fraction in the granulation fluid[27,22]. However, the MCC content of our pellets was low and additionally, the base excipient, Ludiflash®, is composed of different powders. The varying solubilities (in water and ethanol) and the swelling capacities of the individual components suggest complex interactions between the powders and the granulation liquid.

The results of the friability tests indicated that 20% ethanol was not suitable as granulation liquid, since the pellets showed a weight loss greater than 1%, thereby, not fulfilling the requirements. This might be due to the high solubility of mannitol in the granulation liquid: mannitol was likely to be transported toward the pellet surface and recrystallize during tray drying[1], leading to irregularities of the formerly smooth surface that were more prone to attrition. All other formulations investigated exhibited a weight loss well below 1%.

Finally, the outer and the inner morphology of pellets, prepared with 30 and 40% ethanol, was qualitatively analyzed using electron microscopy. The drug-free pellets did not show significant differences depending on the ethanol concentration with respect to the surface morphology (Figure 1 A1 and B1). Small differences, however, could be detected with respect to the internal morphology (Figure 1 A2, B2, A3, and B3). The pellets prepared with 40% ethanol (Figure 1 B3) seemed to be slightly

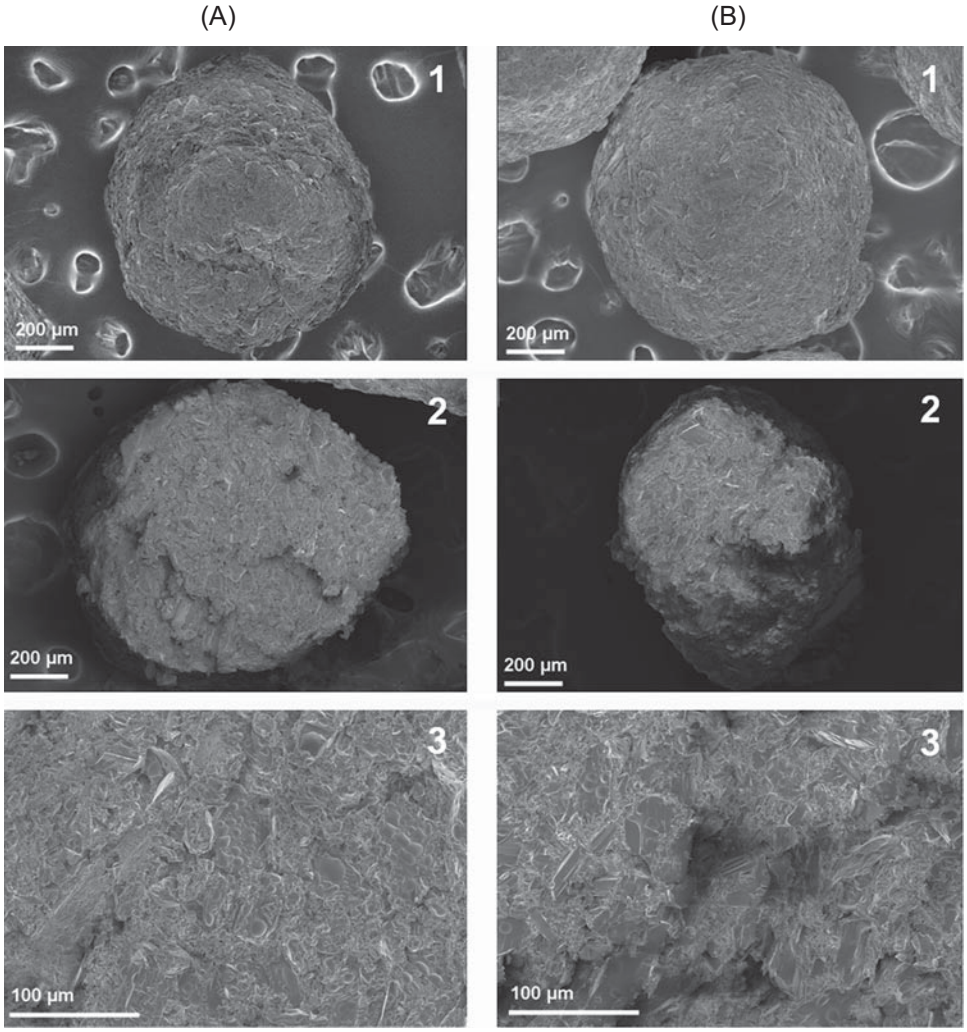

Figure 1. SEM images of unloaded pellets: (A) pellets prepared with 30% ethanol, (A1) surface, (A2) cross cut and (A3) internal morphology; (B) pellets prepared with 40% ethanol, (B1) surface, (B2) cross cut and (B3) internal morphology.

more porous. This might be due to different behavior of the pellets during the drying process.

It can be concluded that wet masses prepared with 30 and 40% ethanol in the granulation liquids demonstrated the best suitability for the extrusion/spheronization process of pharmaceutical pellets. Therefore, these formulations were further investigated in combination with the model drugs.

Preparation of the drug-loaded pellets

Preparation of paracetamol pellets

In the first part of this study, Ludiflash® combined with MCC (Avicel® PH 101) was loaded with paracetamol in different concentrations (i.e. 20, 30, 40 and 50%). The list of the formulations and the corresponding conditions are provided in Table 2.

In addition to the effects for the drug-free pellets (see above), the following effects were assumed to occur during pellet preparation: Paracetamol was wetted by water and ethanol, as contact angle measurements showed that paracetamol exhibits contact angles below 90°. During the wetting step, paracetamol dissolved in water and ethanol with a solubility of 14.3 g/l in water and 143 g/l in ethanol, respectively. It is assumed that during drying paracetamol was transported toward the pellets' surface (due to its solubility in the evaporating liquid) and crystallized. Para F1-F4 refers to formulations that were wetted with 30% ethanol and extruded with a constant screw speed. With increasing drug content, the necessary spheronization time to achieve pellets with a spherical shape, increased from 40 to 90 s. In formulations Para F5–F8, where the process was carried out with 40% ethanol and extruded under the same conditions, no influence of the paracetamol content on the necessary spheronization time was found. Parameter details for all formulations are listed in Table 3.

The yield of the paracetamol pellets in the desired size range decreased with increasing paracetamol content for pellets prepared with 30% ethanol (i.e. from 70.4 to 51.3%). This was attributed to the formation of large pellets. The final pellet size distribution is governed by the extrudate properties, such as the presence of circumferential fracture[28]. Furthermore, the rheological

Table 2. Formulation components and granulation liquid.

Abbreviation	Ludiflash® content (%(w/w))	Avicel® PH 101 content (%(w/w))	Paracetamol content (%(w/w))	Ibuprofen content (%(w/w))	Ethanol content (%(w/w))
Para F1	70	10	20		30
Para F2	60	10	30		30
Para F3	50	10	40		30
Para F4	40	10	50		30
Para F5	70	10	20		40
Para F6	60	10	30		40
Para F7	50	10	40		40
Para F8	40	10	50		40
Ibu F1	70	10		20	30
Ibu F2	60	10		30	30
Ibu F3	50	10		40	30
Ibu F4	40	10		50	30
Ibu F5	70	10		20	40
Ibu F6	60	10		30	40
Ibu F7	50	10		40	40
Ibu F8	40	10		50	40

Table 3. Process parameters applied in the formulation design.

	Wetting		Extrusion		Spheronization		
Abbreviation	Amount of granulation liquid (g)	Moisture content of wet mass (%)	T (°C)	RPM	Time (s)	RPM	Moisture content of wet pellets (%)
Para F1	31	23.10	23.7–24.9	81.7	40	597	21.06
Para F2	31	22.70	23.5–24.8	81.9	60	608	20.99
Para F3	30	22.23	24.0–25.6	80.7	60	608	19.94
Para F4	30	22.70	23.3–24.1	81.4	90	605	20.32
Para F5	29	21.22	23.7–24.6	80.3	50	602	19.03
Para F6	29	21.71	23.5–24.5	80.2	50	604	20.26
Para F7	28	20.14	24.0–25.9	80.4	60	598	17.19
Para F8	30	21.41	23.6–24.2	81.7	50	597	18.75
Ibu F1	32	23.73	23.8–24.3	82.7	40	605	20.72
Ibu F2	25	25.18	24.2–24.7	82.8	60	609	21.92
Ibu F3	32	22.72	24.0–24.6	81.5	40	601	20.57
Ibu F4	32	22.24	23.7–24.3	82.3	40	600	19.77
Ibu F5	33	23.75	23.9–24.4	82.5	40	611	20.75
Ibu F6	33	22.81	24.1–24.6	82.7	60	604	19.76
Ibu F7	34	23.54	24.3–24.9	83.1	40	605	19.90
Ibu F8	32	22.93	23.7–24.7	81.5	40	605	18.63

properties (i.e. deformability vs. brittleness) of the extrudates play a crucial role during spheronization. It can be assumed that the different size distributions, correlated to varying API contents, were rather caused by changes in the extrudate deformability than by distinct circumferential fracture shapes, since the process parameters altering extrudate fracture[28] were kept constant. No clear trend correlating the yield and the drug loading was detected for pellets produced with 40% ethanol (i.e. 59.7, 39.1, 46.25 and 61.9% for Para F5, F6, F7 and F8). This is due to extensive liquid movement during extrusion, which yielded in extrudates varying in the moisture content. Typically, this results in broad particle size distributions after spheronization. Moreover, recrystallization might occur during spheronization due to solvent evaporation thereby influencing the pellet size distribution. Since for all paracetamol formulations the moisture contents of the wet mass and the pellets after spheronization showed similar values (Table 3), recrystallization is very unlikely to have been occurred.

In general, the yield was higher for pellets prepared with 30% ethanol (i.e. 70.3, 69.7, 63.0 and 51.29% for Para F1, F2, F3 and F4) than for those prepared with 40% ethanol (i.e. 59.7, 39.1, 46.25 and 61.9% for Para F5, F6, F7 and F8). A drug loading of 50% was an exception, which, however, is likely to be due to the longer spheronization time of Para F4 which aided the formation of large pellets.

Pellets containing more than 50% of paracetamol could not be successfully produced. Spheronization was impossible and yielded mainly in rods (even after prolonged spheronization times, data not shown). Thus, only formulations up to a drug loading of 50% were further investigated.

Preparation of ibuprofen pellets

In the second part of the study, the extrusion/spheronization process for the preparation of ibuprofen pellets with a drug content of 20, 30, 40 and 50% (process parameters see Table 2) was evaluated. Ibuprofen sparingly dissolves in water but is soluble in ethanol with a solubility of 667 g/l ethanol. From the contact angle measurements, it was found that ibuprofen was well wetted by ethanol (contact angle well below 90°) and sparingly wetted by water (contact angle around 90°). It is assumed that during drying significant amounts of ibuprofen were transported toward the outer surface of the pellets where the API recrystallized and formed solid bridges.

All formulations were successfully extruded and spheronized. Details of the ibuprofen formulations are provided in Table 3.

For Ibu F1-F4 the yield decreased with increasing ibuprofen contents (i.e. from 83.5 to 57.3%) due to the production of small pellets. In contrast, the decrease of the yield for Ibu F5–F8 (i.e. from 62.2 to 55.5%) was due to formation of large pellets. These different observations might be due to diverse conditions (binding, deformability) inside the extrudates resulting in different rheological properties. Again, the effect of recrystallization during spheronization on the final pellet size distribution is negligible, since the moisture contents of the pellets after spheronization showed similar values in comparison to the wet masses (Table 3). Thus, recrystallization was not expected to have been occurred.

In summary, it was found that lower amounts of ethanol, i.e. 30%, in the granulation liquid resulted in controllable process conditions.

Characterization of drug-loaded pellets

Pellet size and shape

For each batch prepared with 30% ethanol, a minimum of 500 pellets of the yield fraction (i.e. between 0.8 and 1.25 mm) were examined via image analysis. The median Ferret's diameter and the median AR were determined (Table 4). All Ferret's diameters were above 1.25 mm which might be due to the 2D image analysis method. For the paracetamol formulations, all ARs were acceptable (i.e. below 1.2) with the exception of Para F2. Ibuprofen pellets showed somewhat higher ARs (above 1.2) except for Ibu F2. An AR ≤ 1.2 is required to reproducibly fill pellets into capsules[29], and is thus, set as an acceptance criterion.

Pellet morphology

The pellet surface morphology, as well as the internal morphology of the formulations with the highest drug loadings possible (i.e. 30% ibuprofen and 50% paracetamol), were investigated via SEM (Figure 2 and 3).

Paracetamol pellets prepared with either 30 or 40% ethanol showed a crystalline surface (Figure 2 A1, A2, B1, and B2). From these images, it cannot be clearly concluded whether the ethanol fraction influenced the amount of crystals present on the surface or not. The cross section area of the paracetamol pellets (Figure 2 A3 and B3) appeared to be crystalline as well. The internal morphology (Figure 2 A4 and B4) did not exhibit a distinctive porous system.

The surface of the ibuprofen pellets (Figure 3 A1, A2, B1, and B2) was crystalline and qualitatively very similar

Table 4. Results of the image analysis for the drug-loaded pellets.

Abbreviation	d_{Fer} (mm)	AR (–)
Para F1	1.76	1.19
Para F2	1.76	1.24
Para F3	1.54	1.15
Para F4	1.58	1.15
Ibu F1	1.82	1.27
Ibu F2	1.63	1.16
Ibu F3	1.63	1.31
Ibu F4	1.71	1.22

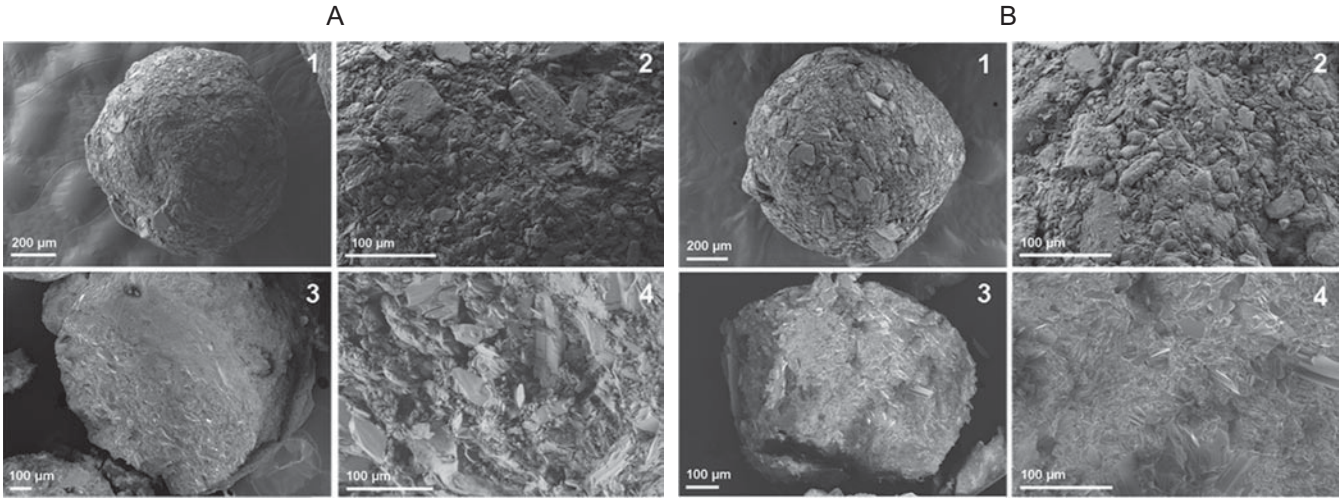

Figure 2. SEM images of the paracetamol loaded pellets: (A) paracetamol pellets prepared with 30% ethanol (i.e. Para F4), (A1) surface, (A2) detailed surface morphology, (A3) cross cut and (A4) internal morphology; (B) paracetamol pellets prepared with 40% ethanol (i.e. Para F8), (B1) surface, (B2) detailed surface morphology, (B3) cross cut and (B4) internal morphology.

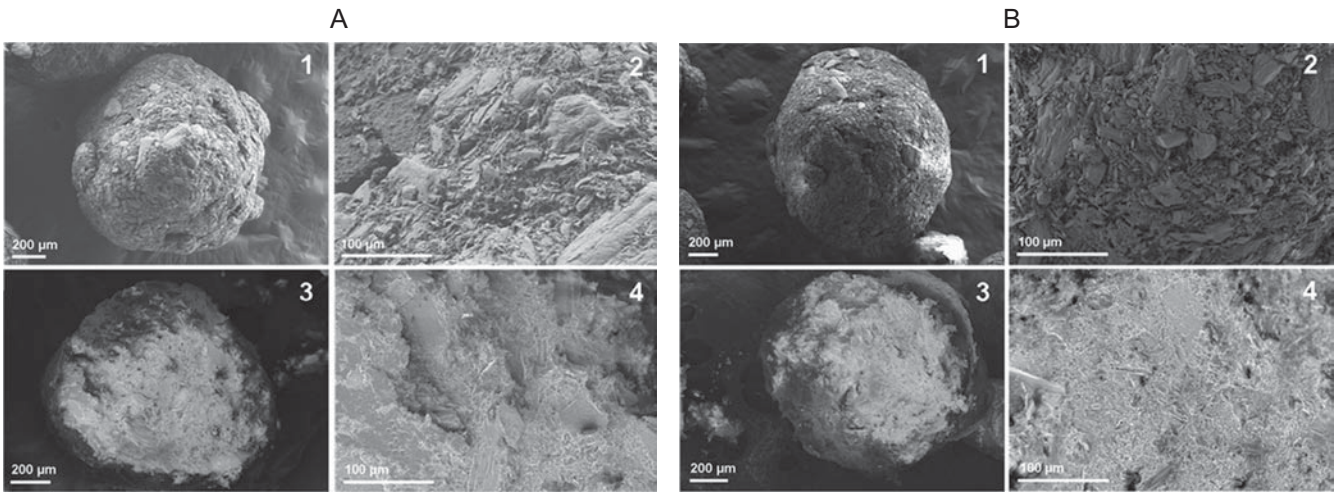

Figure 3. SEM images of the ibuprofen loaded pellets: (A) ibuprofen pellets prepared with 30% ethanol (i.e. Para F4), (A1) surface, (A2) detailed surface morphology, (A3) cross cut and (A4) internal morphology; (B) ibuprofen pellets prepared with 40% ethanol (i.e. Para F8), (B1) surface, (B2) detailed surface morphology, (B3) cross cut and (B4) internal morphology.

to that of the paracetamol pellets (Figure 2 A1 and B1). Examining the cross section area (Figure 3 A3 and B3) and the internal morphology (Figure 3 A4 and B4) pores could not be clearly identified.

For both paracetamol and ibuprofen formulations, it was not possible to point out any clear correlation of the ethanol fraction in the granulation fluid and the final pellet morphology from the SEM investigations. Further studies are required.

Pellet disintegration

Pellet disintegration times are presented in Table 5. All pellet samples of the formulations containing paracetamol, disintegrated within 10 min in de-ionized water at 37.5 ± 0.5°C. For paracetamol pellets produced with 40% ethanol, the disintegration times were slightly higher than for those prepared with 30% ethanol. This might be due to the different recristallization behavior of the (partially) dissolved API during the drying process. This assumption will be investigated in detail in future work. For paracetamol pellets, no clear influence of the drug loading on the disintegration time was observed.

Pellet samples with more than 30% ibuprofen did not entirely disintegrate in all tubes (Table 5). This could be attributed to the poor solubility of ibuprofen in water, preventing water from entering the pellet. Hence, water could not reach all the disintegrant particles. However, the ethanol content of the granulation liquid did not influence the disintegration behavior of the ibuprofen pellets.

In vitro *drug release characteristics*

In vitro drug release characteristics of the paracetamol formulations are shown in Figure 4. Neither the drug content, nor the ethanol fraction in the granulation fluid affected the drug release behavior to a great extent.

Drug loading of pellets prepared with 30% ethanol slightly influenced the drug liberation (Figure 4A). The

Table 5. Disintegration times and tensile strength of paracetamol and ibuprofen pellets. The statistical tests demonstrated a significant influence of the API on the tensile strength ($P < 0.05$).

Abbreviation	Disintegration time [min]	Tensile strength (MPa) ± SD (MPa)
Para F1	8.67	3.51 ± 0.693
Para F2	7.90	3.41 ± 0.676
Para F3	8.87	3.17 ± 0.813
Para F4	8.20	2.97 ± 0.658
Para F5	9.67	3.88 ± 1.080
Para F6	9.72	3.73 ± 0.848
Para F7	9.40	3.18 ± 0.720
Para F8	9.28	2.70 ± 0.684
Ibu F1	8.50	1.74 ± 0.482
Ibu F2	9.00	1.55 ± 0.338
Ibu F3	>10.0	1.59 ± 0.526
Ibu F4	>10.0	1.35 ± 0.342
Ibu F5	9.50	2.21 ± 0.675
Ibu F6	8.95	1.78 ± 0.369
Ibu F7	>10.0	1.67 ± 0.396
Ibu F8	>10.0	1.28 ± 0.377

formulations with the lowest paracetamol content (i.e. Para F1) clearly released lower amounts of API within the first 20 min. However, after 30 min more than 80% of paracetamol was found in the dissolution media for all formulations, which is in accordance with the requirements of the USP. Pellets prepared with 40% ethanol (i.e. Para F5–F8) exhibited a slightly slower drug release (Figure 4B) than pellets prepared with 30% ethanol, which correlates to the somewhat higher disintegration times (Table 5). As soon as pellets disintegrate, the entire drug is released and the dissolution profiles are a function of the drug's solubility. Again, the formulation with the lowest drug loading (i.e. Para F5) showed the slowest liberation kinetics during the first 20 min. After 30 min, more than 80% of the API was liberated except for Para F7. The high standard deviations for formulations containing

20% paracetamol (i.e. Para F1 and Para F5) might derive from inhomogeneities within the vessel which become more evident for low API loadings.

Since ibuprofen is not soluble in acidic media, negligible dissolution occurs in the stomach. However, after the pH is shifted by adding the phosphate buffer, ibuprofen was released within 2 h (Figure 5). The drug release decreased with increasing ibuprofen content, again correlating with the disintegration behavior. The ethanol content of the granulation liquid, however, influenced the release characteristics only slightly. A higher ethanol concentration marginally decreased the amount of released ibuprofen. The prescription for ibuprofen release of the USP is met by formulations with a drug loading up to 30%: For formulations prepared with 30% ethanol, more than 80% of API was released after 40 min in buffer (Ibu F1) and after 50 min (Ibu F2). For pellets produced with 40% ethanol, the same amount was released after 50 min (Ibu F5) and after 60 min (Ibu F6). The results of formulation Ibu F3, F4, F7 and F8 were not in agreement with the specification of the USP, since the time required to release more than 80% of the API exceeded 60 min (i.e. 80 min for Ibu F3 and F4, 100 min for Ibu F7 and even 110 min for Ibu F8).

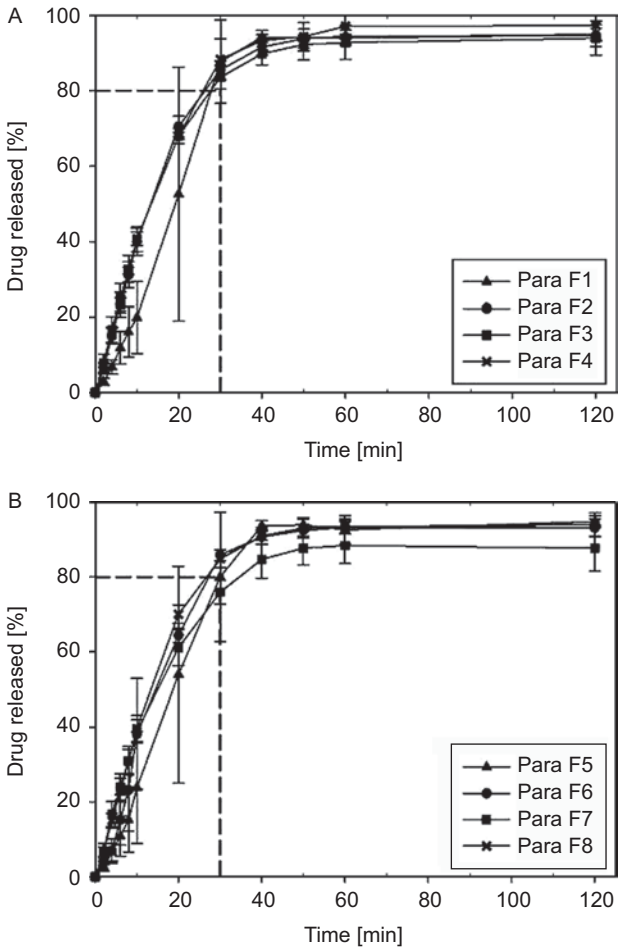

Figure 4. *In vitro* drug release characteristics of paracetamol pellets with different paracetamol loadings (A) prepared with 30% ethanol (B) prepared with 40% ethanol. Dashed lines indicate the requirements of the USP. Mean values ± S.D. $n = 6$.

In summary, the *in vitro* drug release characteristics of all pellet formulations were mainly governed by the disintegration behavior, which is in turn impacted by the solubility and fraction of the model drug (and of the used excipient).

Mechanism of drug release

For investigation of the drug release mechanism, the dissolution data of the first 30 min in HCl were applied for paracetamol pellets. For ibuprofen formulations, the data of the first 60 min in buffer were used. Data analyses based on three different models (i.e. zero order kinetics, first order kinetics and the Weibull model) were performed. Additionally, portions of the release profiles, where $A_t^* \leq 0.6$, were fitted according to the Korsmeyer-Peppas approach. The results of the data analyses are summarized in Table 6.

Comparing coefficients of correlation (R^2), the paracetamol release profiles were best fitted to the Weibull as well as the Korsmeyer-Peppas model. The values for τ (i.e. the time after which 63.2% of the API are dissolved

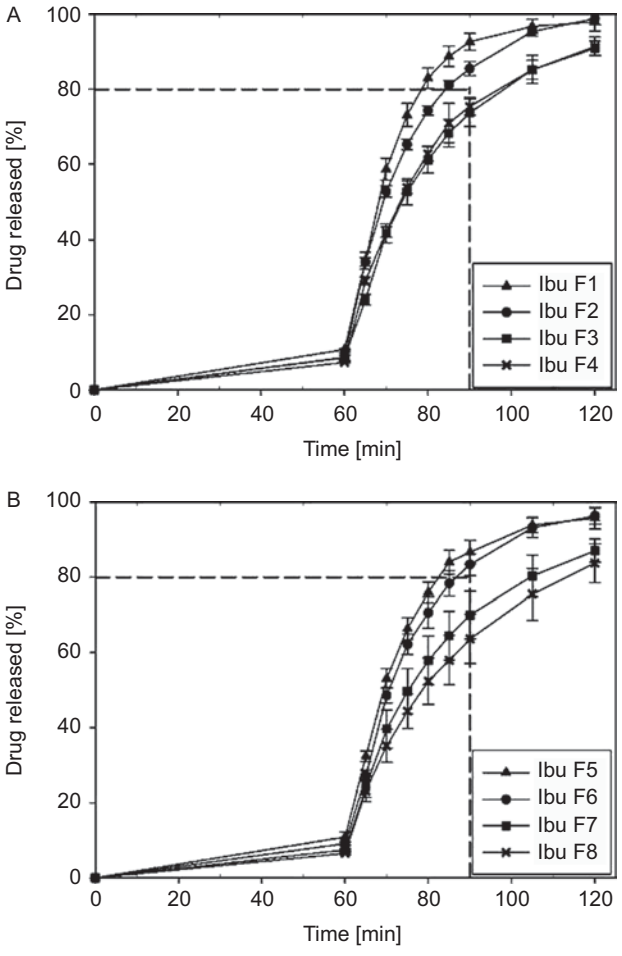

Figure 5. *In vitro* drug release characteristics of ibuprofen pellets with different ibuprofen loadings (A) prepared with 30% ethanol (B) prepared with 40% ethanol. Due to the pH-dependent solubility of ibuprofen drug release started after 2 h (120 min) when the pH was increased. Dashed lines indicate the requirements of the USP. Mean values ± S.D. $n = 6$.

Table 6. Results of dissolution data analyses.

	Zero order			First order			Weibull			Korsmeyer-Peppas			
Abbreviation	R^2	$A_0^* \times 10^{-2}$	$k_0 \times 10^{-2}$ (min^{-1})	R^2	ln A_0^*	$k_1 \times 10^{-2}$ (min^{-1})	R^2	τ (min)	β	R^2	$K \times 10^{-2}$ (min^{-n})	n	Release mechanism
Para F1	0.9882	−4.947	2.969	0.8762	−3.035	10.83	0.9902	21.85	1.836	0.9984	1.07	1.300	Super Case II
Para F2	0.9707	4.642	2.940	0.7737	−2.117	7.730	0.9997	17.30	1.245	0.9997	3.36	1.075	Super Case II
Para F3	0.9669	6.171	2.813	0.7743	−2.007	7.170	1.000	17.82	1.144	0.9996	4.20	0.9862	Super Case II
Para F4	0.9780	4.497	2.982	0.7613	−2.128	7.830	0.9987	17.15	1.247	0.9994	3.25	1.101	Super Case II
Para F5	0.9938	−3.719	2.786	0.8465	−3.040	10.82	0.9988	22.85	1.638	0.9975	1.11	1.299	Super Case II
Para F6	0.9600	−0.7332	3.169	0.7783	−2.679	9.950	0.9928	18.94	1.463	0.9922	0.56	1.821	Super Case II
Para F7	0.9585	6.497	2.527	0.7304	−2.071	7.080	0.9986	20.97	1.029	0.9968	3.99	0.9903	Super Case II
Para F8	0.9708	4.599	2.918	0.7738	−2.126	7.730	0.9997	17.53	1.238	0.9997	3.33	1.075	Super Case II
Ibu F1	0.9128	22.49	1.352	0.7463	−1.579	3.110	0.9793	22.94	1.018	0.8996	5.85	0.7699	Anomalous
Ibu F2	0.9216	20.24	1.237	0.7213	−1.716	3.210	0.9843	27.91	0.8586	0.9262	8.03	0.6282	Anomalous
Ibu F3	0.9582	14.69	1.083	0.8042	−1.891	3.180	0.9775	42.44	0.8620	0.9305	5.03	0.6940	Anomalous
Ibu F4	0.9522	15.69	1.103	0.7506	−1.903	3.280	0.9835	40.02	0.8161	0.9549	7.82	0.5657	Anomalous
Ibu F5	0.9316	20.61	1.263	0.7708	−1.620	3.030	0.9746	27.16	0.9330	0.8663	6.22	0.7162	Anomalous
Ibu F6	0.9432	17.01	1.240	0.7833	−1.788	3.260	0.9807	31.77	0.9477	0.8932	3.88	0.8436	Case II
Ibu F7	0.9568	14.06	1.023	0.7813	−1.968	3.230	0.9816	47.72	0.8092	0.9639	6.23	0.6078	anomalous
Ibu F8	0.9600	12.81	0.9217	0.7718	−2.069	3.200	0.9825	59.85	0.7563	0.9762	6.47	0.5634	Anomalous

Table 7. Pellet densities and porosities.

Abbreviation	True density (g/cm³)	Specific pore volume (open pores) (cm³/g)[a]	Apparent density (g/cm³)[b]	Porosity (%)[b]
Para F4	1.391	0.149	1.14	17.0
Para F8	1.392	0.169	1.11	18.7
Ibu F2	1.349	0.187	1.07	19.9
Ibu F6	1.352	0.179	1.08	19.4

[a]Obtained from the Hg porosimetry measurements.
[b]Calculated from the He-density and the results of the Hg porosimetry measurements.

in the dissolution medium) were highest for the lowest drug loading. For drug loadings ranging from 30 to 50% τ values were similar, where those for pellets prepared with 40% ethanol were slightly higher. The release exponents determined by applying the Korsmeyer-Peppas model indicated Super Case II transport mechanism for all paracetamol formulations. API release from ibuprofen pellets was best described by the Weibull model (R^2 higher than 0.97). The values for τ increased with increasing drug loading and were markedly elevated at API contents of 40 and 50%. Again, τ was higher for formulations prepared with 40% ethanol. The comparatively low coefficients of correlation for the Korsmeyer-Peppas fits derived from the fact that when the buffer was added to the dissolution medium small amounts of ibuprofen were already dissolved. Consequently, the ibuprofen dissolution profiles in buffer do not intersect the origin. The release exponents *n* suggested anomalous transport mechanisms for all ibuprofen formulations except for Ibu F6 where an *n* value of 0.8436 rather indicated a Case II transport.

Pellet friability and tensile strength

All formulations showed a weight loss below 1% after friability testing. For paracetamol pellets, the friability increased with increasing drug loading. No remarkable differences were observed between pellets prepared with 30 and 40% ethanol. The results of the friability test for the ibuprofen pellets did not show any trends with respect to the API content and the granulation liquid.

The tensile strength of paracetamol pellets slightly decreased with increasing drug content when 30% ethanol was used as granulation liquid (Table 5). The same trend could be detected for the higher ethanol content (i.e. 40%; Table 5). Apparently, increasing the API content, thereby lowering the Ludiflash® content, resulted in decreased pellet strength. From the statistical analysis, it was observed that the ethanol content in the granulation fluid significantly influenced only the formulations containing 30% paracetamol.

As expected, the tensile strength of ibuprofen formulations was lower at higher drug loadings, independently on the granulation liquid (Table 5). This fact is attributed to the decreasing Ludiflash® content with increasing drug loading. The type of granulation fluid showed a significant impact on the pellet strength for pellets with drug loadings of 20 and 30%.

Paracetamol pellets exhibited higher tensile strengths than ibuprofen pellets, indicating differences in the pellet morphology despite the apparently similar production technique. From the statistical tests, it was calculated that the type of API showed a significant influence on the tensile strength ($P < 0.050$).

Since the values for the tensile strength were all well above 1 MPa for both, paracetamol and ibuprofen formulations, the produced pellets were considered to exhibit sufficient mechanical stability.

Pellet porosity and density

Pellet formulations with the highest API contents (i.e. Para F4, Para F8, Ibu F2 and Ibu F6) were tested for density and porosity. The results of both, the He-pycnometry and the mercury porosimetry measurements, are summarized in Table 7. The calculation of the apparent density and the porosimetry assumes that the He-density refers to the true density. However, it might be possible that the pellets exhibited closed pores that are not filled with helium during the measurements.

The true densities of all investigated pellets were nearly identical (i.e. 1.391 g/cm³, 1.392 g/cm³, 1.349 g/cm³ and 1.352 g/cm³ for Para F4, Para F8, Ibu F2 and Ibu F6, respectively).

Paracetamol pellets produced with 40% ethanol exhibited a slightly higher porosity than pellets prepared with 30% ethanol (i.e. 17.0% for Para F4 and 18.7% for Para F8). Ibuprofen pellets showed similar values for the porosity (i.e. 19.9 and 19.4% for Ibu F2 and Ibu F6). The porosity of the ibuprofen pellets was slightly higher, which might be caused by the different API loadings or by the varying solubilities of paracetamol and ibuprofen in the granulation liquids. Generally, from the mercury intrusion curves (graphs not shown), it was found that the pore sizes for all samples ranged from 0.1 to 4 μm.

As already seen in the electron microscopy images, the granulation liquid did not influence the pore structure and the density, nor did any of the pellet formulations exhibit a distinctive pore structure.

Conclusions

In this study, the suitability of Ludiflash®, a direct compression aid, for the preparation of pharmaceutical pellets was investigated. A wet extrusion/spheronization process was successfully developed for formulations containing Ludiflash® as main excipient. It was clearly demonstrated that pellets with a spherical shape were prepared without losing the beneficial properties of Ludiflash® (i.e. rapid drug release and high mechanical stability). The disintegration characteristics of the produced pellets were affected by the drug solubility and, in the case of the poorly soluble API (i.e. ibuprofen), on the drug loading. All paracetamol formulations prepared with 30% ethanol released more than 80% of the API within 30 min in hydrochloric acid. Ibuprofen pellets

liberated more than 80% of the drug within 60 min up to a drug loading of 30% in buffer. These formulations were in agreement with the requirements of the USP. Drug release exponents (obtained from the Korsmeyer-Peppas approach) indicated Super Case II transport for all paracetamol formulations and anomalous transport for most ibuprofen formulations. The dissolution rates were mainly governed by the disintegration behavior.

From this work, it can be concluded that pellets containing Ludiflash® as main excipient provide a suitable dosage form for drug administration in children. Individually dosable pellets complied with the requirements of paediatric dosage forms could be achieved, combining (i) a high mechanical stability, (ii) a good mouthfeel and (iii) fast drug release.

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Declaration of interest

The authors report no declarations of interest.

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