European Journal of Pharmaceutics and Biopharmaceutics 75 (2010) 56–62

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

# Development of lipophilic calcium stearate pellets using ibuprofen as model drug

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ARTICLE INFO

*Article history:*
Received 19 August 2009
Accepted in revised form 7 January 2010
Available online 18 January 2010

*Keywords:*
Pellets
Extrusion/spheronisation
Calcium stearate
Ibuprofen
Zero-order release

ABSTRACT

*Introduction:* The aim of the study was the development of lipophilic pellets containing calcium stearate and ibuprofen as model drug. The pellets were produced by a standard wet extrusion and spheronisation technology. As a main target, the pellets should exhibit sufficient mechanical stability, should not disintegrate in an aqueous vehicle and should show a retarded release kinetic. Furthermore, the drug release should be adjusted only by the ratio between drug and excipient without any additional coating procedure.

*Methods:* Different lipids (Precirol®, Compritol®, glyceryl monostearate, magnesium stearate and vegetable calcium stearate) were used as lipophilic pelletisation excipients in extrusion/spheronisation using ethanol/water as granulation liquid. The lipids were combined with ibuprofen as a model drug with pH-dependent solubility in several concentrations (15%, 20% and 25% drug content).

*Results:* Calcium stearate (CS) was found to be a suitable carrier substance for the preparation of spherical pellets (AR $\leqslant$ 1.2). As pellet properties, the mean particle random diameter, surface area, porosity, tensile strength and dissolution profile were determined. By variation of the die plate (1 mm, 0.8 mm and 0.5 mm) and variation of the ethanol/water composition (96% and 50%) of the granulation liquid, pellets in the size range from 800 to 1250 μm with a sufficient drug loading capacity up to 20%, a zero-order drug release and high mechanical stability could be produced.

*Conclusion:* The results demonstrated that calcium stearate can be used as pelletisation excipient for slow release formulations by a wet extrusion/spheronisation technique. With this technology, a continuous production of slow release multiple unit preparations will be possible without further coating steps.



## 1. Introduction

Pellets are described as geometrically defined agglomerates produced by the pelletisation process. Due to agglomeration during this process, the fine excipient and drug powders are converted into small, spherical or semi-spherical and free flowing units. Today, many techniques are available to produce pellets. Among them, solution/suspension layering, powder layering, direct pelletisation and extrusion/spheronisation are established methods used in the pharmaceutical industry [1]. In this study, we particularly focus on the wet extrusion/spheronisation technique. Microcrystalline cellulose (MCC) is the "gold standard" as extrusion/spheronisation excipient for the preparation of controlled release pellets. MCC shows plasticity and good rheological properties when wetted, and the drug release is actively controlled via the diffusion of the polymer [2–5].

In comparison with MCC, lipids are promising alternative excipients for the preparation of multiple units drug delivery systems. They are natural excipients, are biodegradable and have a favourite toxicity profile. Additionally, they have the capacity to suppress bitterness of drugs and can enhance the bioavailability of poorly soluble drugs [6,7]. Glyceryl monostearate has been introduced as lipid pelletisation aid as an alternative for MCC. It is an organic molecule, insoluble in water, but with emulsifying and plastifying properties. Basit et al. have shown for water-insoluble drugs (ranitidine) that formulations incorporating barium sulfate and glyceryl monostearate (GMS) with or without MCC resulted in relatively spherical pellets of narrow size distribution. The pellets showed sufficient mechanical properties, and the drug was released within 15 min, regardless of the pellet formulation [8]. Later work by Chatchawalsaisin et al. provided evidence that the presence of GMS, using barium sulfate and diclofenac sodium as model drugs resulted in acceptable spherical pellets at drug contents between 10% and 90%. The porosity was dependent on the amount of GMS used in the formulations and demonstrated porosity levels of less than 10% even for high concentrations of GMS. The in vitro dissolution from GMS formulations showed that after 3 h, between 80% and 100% of the drug was released, thus exhibiting immediate release profiles. Further work by Chatchawalsaisin reported that the drug release was only controlled by the solubility of the drug and not by the presence of GMS [9,10]. Due to many investigations,

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doi:10.1016/j.ejpb.2010.01.005

lipids are also preferable excipients for melt pelletisation. In this case, the product temperature is raised to the binder's melting point by heating the jacket of the apparatus or by increasing the impeller speed of a high-shear mixer. The binder melts during the process, promoting agglomeration or incorporating the drug in order to achieve a sustained drug release without any coating procedure [11–16]. An alternative recommended area for the application of lipids is the solid lipid extrusion, where lipid binders with similar melting ranges are extruded at temperatures slightly below the melting ranges [17–19].

In the current study, we investigated the use of vegetable calcium stearate as the main excipient for the preparation of sustained release pellets. Commercially available calcium stearate is a mixture of the insoluble calcium salt of stearic and palmitic acid and acts as non-toxic stabilizer and lubricant in the pharmaceutical industry. In comparison with GMS, calcium stearate shows no emulsifying properties. Therefore, water/ethanol mixtures are utilized for the wetting step.

The pellets have been produced by a standard wet extrusion technology to take advantage of a low temperature process which preferably takes place at room temperature. As a main target, the pellets should exhibit sufficient mechanical stability, should not disintegrate in an aqueous vehicle and should show retarded release kinetics. Furthermore, the drug release should be adjusted only by the ratio between drug and excipient without any additional coating procedure. In detail, we evaluated the impact of the process parameters, the pellet formulation and the ethanol content in the granulation liquid on the final pellet characteristics. Ibuprofen belonging to the BCS class II was utilized as model system and used in concentrations compared to paediatric products on the market, i.e., 200 mg partial dose.

## 2. Materials and methods

### 2.1. Materials

Ibuprofen, of European Pharmacopoeia grade, was a gift from G.L. Pharma GmbH, Lannach, Austria with a volume mean particle size of 255.9 μm. Magnesium stearate (Apoka, Vienna, Austria; volume mean particle size 8.35 μm), Precirol ATO 5 (Gattefosse, Weil am Rhein, Germany; volume mean particle size of 40 μm), Compritol 888 (Gattefosse, Weil am Rhein, Germany; volume mean particle size of 40 μm), glycerol monostearate (Apoka, Vienna, Austria; volume mean particle size 18.23 μm) and vegetable calcium stearate (stearic acid 44% and palmitic acid 54%, Pharm. Eu. quality; Werba – Chem GmbH, Vienna, Austria; volume mean particle size of 16.62 μm) were used as lipophilic binders and used as received. The volume mean particle sizes were determined via laser diffraction (Mastersizer 2000, Malvern Instruments Ltd, Malvern, United Kingdom). As binding liquid ethanol (Merck, Darmstadt, Germany) and mixtures of ethanol/purified water (50% w/w) were used. The in vitro release was carried out with 0.1 N hydrochloric acid (Merck, Darmstadt, Germany) and tris-phosphate-dodeca-hydrate buffer as gastric and intestinal dissolution media. For the high performance liquid chromatography (HPLC) analysis, acetonitril (Merck, Darmstadt, Germany), potassium dihydrogen phosphate (Carl Roth GmbH, Karlsruhe, Germany) and orthophosphoric acid 85% (Merck, Darmstadt, Germany) were used as mobile phase. The HPLC column YMC-Pack DDS-AQ RP-18 was purchased from YMC Co., Ltd., Japan.

### 2.2. Methods

#### 2.2.1. Pre-formulation of unloaded lipid pellets

The lipids used in this work are given in Table 1. The powdered substances (100 g) were mixed in a planetary mixer (Kenwood Chief, Seligenstadt, Germany). The agglomeration liquid ethanol 96% was added manually by pouring onto the dry powders over a period of 10 min. The process was stopped twice to scrape down the sides of the bowl. For the determination of the correct liquid level, the moisture content of the wet powder mass was measured with a halogen moisture analyzer (Mettler, Toledo, Greifensee, Switzerland). The wet powder mass was transferred into the single-screw extruder and immediately extruded with a constant screw speed of 82 rpm at room temperature (Extruder Pharmex T35, Gabler Maschinenbau, Lübeck, Germany). The extrusion time was kept short (2 min); therefore, no external cooling system was necessary. As die a multi hole end extrusion plate (0.8 mm diameter, 2 mm in length, 895 holes) was utilized. The screw exhibited a diameter of 60 mm maximum and 40 mm minimum. The extrudates (60 g) were transferred into a spheroniser (Sphäromat 250T, Gabler Maschinenbau GmbH, Lübeck, Germany) with a cross-hatched friction plate of 250 mm diameter and were spheronised for 2–6 min (Sphäromat, 250T, Gabler Maschinenbau, Lübeck, Germany) with a rotation speed of 676 rpm. The drying step was carried out in an oven (Heraeus Type 5042 E, Hanau, Germany) for 24 h at 40 °C.

**Table 1**
Lipids used for the extrusion/spheronisation process.

| Lipid binder | Melting point (°C) | Pellet shape |
|---|---|---|
| Magnesium stearate | 117–150 | Non-spherical pellets |
| Precirol ATO 5 | 52–55 | Spherical pellets |
| Compritol 888 | 69–74 | Spherical pellets |
| Glycerol monostearate | 55–60 | Non-spherical pellets |
| Calcium stearate | 149–160 | Spherical pellets |

#### 2.2.2. Preparation of the drug-loaded lipid pellets

Out of the results of the pre-formulations, vegetable CS was used for further investigations. Therefore, CS was mixed with ibuprofen as model drug (100 g; 15%, 20% and 25% drug content) for 20 min in a cube blender (UAM, Pharmatest, Hainburg, Germany). As granulation liquid ethanol, respectively, ethanol/water was used in two different concentrations, i.e. 96% and 50% (Kenwood Chief, granulation time: 10 min, 60 rpm). During the granulation step, the basic materials were scraped from the mixing bowl walls twice to ensure equal distribution of the liquid. For the determination of the liquid level, the moisture content of the wet powder mass was evaluated by a halogen moisture analyzer (Mettler, Toledo, Greifensee, Switzerland). The wet drug/lipid mixtures were transferred into the single-screw extruder and immediately extruded through three variable multi hole end extrusion plates, i.e. (i) 1.0 mm diameter, 2 mm in length, 895 holes, (ii) 0.8 mm diameter, 2 mm in length, 895 holes and (iii) 0.5 mm diameter, 2 mm in length, 895 holes (Extruder Pharmex T35, Gabler Maschinenbau, Lübeck, Germany). The screw, with a diameter of 60 mm maximum and 40 mm minimum, was driven at a constant speed of 80 rpm. The extrusion time was set to 2 min; therefore, no external cooling system was necessary. Consequently, 60 g extrudates were transferred into a spheroniser (Sphäromat 250T, Gabler Maschinenbau GmbH, Lübeck, Germany) with a cross-hatched friction plate of 250 mm in diameter and spheronised for 2 min at 610–987 rpm. Finally, the pellets were spreaded on stainless steel trays and dried in an oven for 24 h at 40 °C to constant weight (Heraeus Type 5042 E, Hanau, Germany). An overview of the formulations and parameters is given in Tables 2 and 3.

#### 2.2.3. Pellet characterisation

*2.2.3.1. Sieving, image analysis.* The sieve analyses were carried out according to the European Pharmacopeia (2.9.38) to define the following fractions as yield: (i) 1250–1000 μm, (ii) 1000–800 μm

**Table 2**
(A) Formulation components, granulation liquid and die plates used for the extrusion experiments. (B) Composition of the pellet formulations as a % (w/w) of the final dry pellets and the amount of ethanol (ethanol/water) added to 100 g of the powder mixtures.

| Abbreviation | Drug/excipient | Granulation liquid | Die plate (diameter/length) (mm/mm) |
|---|---|---|---|
| *A* | | | |
| F1 | Ibuprofen CS | 96% ethanol | 1/2 |
| F2 | Ibuprofen CS | 96% ethanol | 1/2 |
| F3 | Ibuprofen CS | 96% ethanol | 1/2 |
| F4 | Ibuprofen CS | 96% ethanol | 0.8/2 |
| F5 | Ibuprofen CS | 96% ethanol | 0.8/2 |
| F6 | Ibuprofen CS | 96% ethanol | 0.8/2 |
| F7 | Ibuprofen CS | 96% ethanol | 0.5/2 |
| F8 | Ibuprofen CS | 96% ethanol | 0.5/2 |
| F9 | Ibuprofen CS | 96% ethanol | 0.5/2 |
| F10 | Ibuprofen CS | 50% ethanol | 0.8/2 |
| F11 | Ibuprofen CS | 50% ethanol | 0.5/2 |

| Abbreviation | Quantity of ibuprofen (%) | Quantity of CS (%) | Quantity of granulation liquid (g) |
|---|---|---|---|
| *B* | | | |
| F1 | 15 | 85 | 22 |
| F2 | 20 | 80 | 17 |
| F3 | 25 | 75 | 14 |
| F4 | 15 | 85 | 21 |
| F5 | 20 | 80 | 18 |
| F6 | 25 | 75 | 15 |
| F7 | 15 | 85 | 21 |
| F8 | 20 | 80 | 18 |
| F9 | 25 | 75 | 17 |
| F10 | 20 | 80 | 41 |
| F11 | 20 | 80 | 22 |

and (iii) 800–400 μm. Each batch was sieved for 5 min with five analytical DIN sieves (according to the DIN 166165) of 400–1250 μm aperture with an agitation of 50 vibrations per min till the endpoint was reached (Type RV, Retsch KG, Haan, Germany). Subsequently, a representative sample of each fraction was obtained for image analysis by using a rotary cone sample divider. Pellets were placed on a dark background and mechanically separated. The image analysis was carried out using a digital camera (Canon EOS D30, Canon Europa NV, Amstelveen, Netherlands) and sophisticated image processing software (ImageJ, National Institute of Health, Bethesda, USA). The Ferret's diameter and the aspect ratio (AR) were determined.

*2.2.3.2. Dissolution profiles.* The release of ibuprofen from the different formulations was examined in vitro by the USP XXVIII rotating basket method ⟨7 1 1⟩. The apparatus (PharmaTest Type PTWS III C, Hainburg, Germany) was used at a release temperature of 37 ± 0.5 °C and a stirring speed of 100 rpm. The vessels were filled with 0.1 N hydrochloric acid (750 ml), after two hours, 250 ml tris-phosphate-dodeca-hydrate buffer was added to switch the pH from 1.2 to 6.8. For each formulation pellets containing 200 mg of ibuprofen (according to the partial dose) were filled into the six baskets. Samples of 1 ml were withdrawn from the dissolution medium after 10 min, in order to determine the initial dose, then after 0.5, 1, 2, 3, 4, 5, 6, 7, 8 and 24 h. For each formulation, six replicates were carried out with a weighed amount of approximately 1000 mg pellets from the 1.25–1.0 mm, the 1.0–0.8 mm and 0.8–0.4 mm from the size fractions. Additionally, the withdrawn samples were analysed by a reversed phase high performance liquid chromatography (RP-HPLC).

To investigate the mechanism of release of ibuprofen from the pellet (after the initial dose was released), the data between 5 and 24 h were calculated according a zero-order kinetic equation (Eq. (1)), where $A$ is the percentage of released drug at time $t$ [20]:

$$-dA/dt = k_0 \quad (1)$$

*2.2.3.3. HPLC analysis.* The ibuprofen concentration was determined by a modified USP HPLC method (Ibuprofen Oral Suspension), carried out by a Merck system (AS-4000 Intelligent Auto Sampler, Merck Hitachi, Japan). An analytical column (YMC-Pack DDS-AQ RP-18, 5 μm 250 × 4.0 mm, YMC Co., Japan) was used at 25 °C. The mobile phase consisted of acetonitril and potassium dihydrogen phosphate buffer (60/40 v/v) and was adjusted with orthophosphoric acid at a pH of 3. The samples were centrifuged at 13,200 rpm (Eppendorf Centrifuge 5415C), and 250 μl of every sample was diluted with 750 μl of the mobile phase prior to injection. The injection volume was set 10 μl, the flow rate was 1.2 ml per min. Each sample was analysed twice.

*2.2.3.4. Pellet structure.* The pellets were visualised by an electron microscope (Zeiss Ultra 5, Germany). The particles were fixed on an adhesive SEM plate and coated with chrome under vacuum. The surface morphology and the internal structure of the pellet were visualised in the SEM mode.

*2.2.3.5. Pycnometric density and mercury porosimeter density.* Pycnometric density measurements of the pellets were performed using a helium-pycnometer Quantachrome Ultrapycnometer-1000 T (Odelzhausen, Germany) at 25 °C. The pellets were transferred into a sample chamber of a volume of 20 $cm^3$ and flushed with helium.

**Table 3**
Process parameters applied in the formulation design.

| Abbreviation | Extrusion | | | Spheronisation | | Moisture content of the wet mass before the extrusion process (%) |
|---|---|---|---|---|---|---|
| | Die (diameter mm/length mm/holes) | *T* (°C) | RPM | Time (min) | RPM | |
| F1 | 1/2/895 | 20.4 | 80.8 | 1 | 628 | 14 |
| F2 | 1/2/895 | 20.9 | 80.9 | 2 | 625 | 13 |
| F3 | 1/2/895 | 22.7 | 80.0 | 3 | 628 | 13 |
| F4 | 0.8/2/895 | 20.9–21.7 | 79.2 | 2 | 610 | 15 |
| F5 | 0.8/2/895 | 21.7–22.5 | 80.3 | 2 | 620 | 16 |
| F6 | 0.8/2/895 | 22.4–23.3 | 80.3 | 2 | 680 | 16 |
| F7 | 0.5/2/895 | 21.0–22.4 | 79.9 | 2 | 612–976 | 16 |
| F8 | 0.5/2/895 | 23.7–25.7 | 78.4 | 2 | 987 | 16 |
| F9 | 0.5/2/895 | 22.8 | 80.4 | 2 | 970 | 16 |
| F10 | 0.8/2/895 | 19.8 | 89.3 | 2 | 966 | 26 |
| F11 | 0.5/2/895 | 22.4 | 78.5 | 3 | 615 | 26 |

Mercury porosimeter density of the pellets was determined using a Quantachrome Poremaster 60-GT. The pellets were transferred into the sample chamber and evacuated, and the chamber was filled with mercury according to the manufacturer's instructions. By the use of both methods, extended information about pellet porosity can be derived.

*2.2.3.6. Tensile strength and particle random diameter.* Tensile strength and particle random diameter measurements were carried out using a rotational plate–plate rheometer (Physica MCR 501, Anton Paar GmbH, Graz, Austria). The rheometer was used in the normal force mode without rotation. The accuracy of the force was given by the manufacturer (0.002 N). Each pellet (of the 0.8–1 mm fraction yield) was transferred between the plates separately. The upper plate was moved down with a constant velocity of 0.5 μm/s. The fracture was determined as maximum force ($F$) during irreversible plastic deformation until the pellet was fractured. Additionally, the distance between the plates at the onset of compression was taken as particle diameter. The tensile strength ($TS$) was calculated according the following equation (Eq. (2)) including the diameter ($d$) of the pellets [21]:

$$TS = 1,6 \cdot F/\pi \cdot d^2 \quad (2)$$

## 3. Results and discussion

### 3.1. Pre-formulation of unloaded lipid pellets

Powders of pure magnesium stearate, Precirol ATO5, Compritol 888, GMS and CS were processed first by conventional wet granulation, followed by extrusion in a single-screw pharma extruder. The experiments were carried out at room temperature (22–25 °C) which was kept constant during the short extrusion time without using an external cooling system. For the first set of experiments, ethanol 96% was used as granulation liquid. For the extrusion process, a speed of 80 rpm and a die plate of 0.8 mm diameter were selected for all preliminary formulations without drug. The rotational speed of the spheroniser was set to 680 rpm. Magnesium stearate and GMS pellets were found to be not completely spherically and, in most cases, displayed a non-spherical structure. During the spheronisation process, the extruded lipid strands did break into multiple rods but resulted in non-spherical pellets after a spheronisation time of 2–4 min. Additional experiments with a prolonged spheronisation time did not improve the shape of the particles.

In contrast to GMS and magnesium stearate, not only CS but also Precirol and Compritol were found to be appropriate for our low temperature wet granulation and extrusion/spheronisation conditions. The extrudate was successfully rounded by the interaction between the friction plate and the wall at 690 rpm with a spheronisation time between 2 and 4 min. The short spheronisation time demonstrated that the extrudate showed sufficient plasticity for the preparation of spherical pellets.

In comparison with Precirol and Compritol, the sieve analyses demonstrated that CS pellets resulted in the highest yield in the desired size range. Seventy % of the pellet mass was found in the size range of 800–1000 μm. Precirol and Compritol also showed spherical pellets, but an average of 81% and 60%, respectively, of the obtained pellets were larger than 1000 μm. In summary, after visual and analytical evaluation of the pellets, it can be concluded that CS showed the best suitability for our wet extrusion/spheronisation technique under these conditions. Therefore, CS was further investigated in combination with ibuprofen.

### 3.2. Preparation and in vitro release of calcium stearate/ibuprofen pellets

CS, used as pelletisation aid, was loaded with ibuprofen in concentrations of 15%, 20% and 25%. The pellets were expected to show a prolonged drug release profile, good taste masking and no drug loss and disintegration in an aqueous solution. After variation of the die plate of the single-screw extruder (1 mm, 0.8 mm and 0.5 mm) and variation of the granulation liquid (ethanol/water mixtures of 96% and 50%), the pellets were characterised and tested for the desired properties as described earlier.

#### 3.2.1. Pellet production and pellet size

The wet extrusion/spheronisation process was robust and easily carried out for all formulations. Pellets consisting of 15–25% ibuprofen according to 85–75% CS were granulated with ethanol/water and extruded through a 1.0-mm die plate (parameter details see Tables 2 and 3). In general, sufficient pellet production in combination with ibuprofen was achieved. The size distribution analysis by sieving resulted in 90% pellet mass in the range of 1000–1250 μm (Table 4a). By variation of the die plate to 0.8 mm, the screw speed and the amount of granulation liquid remained constant. The pellet fraction in a range of 800–1000 μm yielded approximately in 55% (see Table 4b). Finally, a 0.5-mm die plate was used, and 16% moisture content resulted in optimal conditions for extrusion and spheronisation in order to achieve spherical pellets. Consequently, in the range size of 400–800 μm, an excellent yield of 93% pellet mass was reached (Table 4c). For all formulations, the ARs were acceptable, i.e. $\leqslant$1.2 (±0.22 SD).

In addition, no influence of the ibuprofen content on the size and shape of the pellets could be found. However, the amount of granulation liquid required to obtain optimal plasticity of the wet mass decreased with an increasing amount of ibuprofen. When using 50% ethanol/water instead of ethanol 96% as granulation liquid, the moisture content increased from 16% to 26% (see Table 3).

#### 3.2.2. In vitro release studies of ibuprofen/CS pellets

The influence of the particle size and the drug content on the release profile is shown in Fig. 1. For poorly soluble and weak acids like ibuprofen – a BCS class II drug – in general, a negligible dissolution occurs in the stomach. However, the dissolution rate increases with increasing pH. Thus, in vivo nearly complete dissolution occurs in the small intestine [22]. For example, pellets with 15% ibuprofen content showed a negligible drug release dur-

**Table 4**
Size distribution of CS/drug pellets with 15%, 20% and 25 % drug loading: (a) 1-mm die plate; (b) 0.8-mm die plate; (c) 0.5-mm die plate.

| Aperture size (mm) | F1 (%) | F2 (%) | F3 (%) | F4 (%) | F5 (%) | F6 (%) |
|---|---|---|---|---|---|---|
| 1.25 | 66.98 | 19.25 | 60.27 | 29.61 | 44.14 | 18.18 |
| 1.00 | 30.18 | 67.12 | 27.57 | 54.80 | 47.43 | 63.72 |
| 0.80 | 1.82 | 8.62 | 5.76 | 13.40 | 7.63 | 15.83 |
| 0.63 | 0.48 | 2.67 | 2.08 | 1.20 | 0.70 | 1.39 |
| 0.40 | 0.42 | 1.56 | 2.00 | 0.53 | 0.00 | 0.74 |
| Powder mass | 0.12 | 0.8 | 2.32 | 0.46 | 0.00 | 0.13 |
| Median (mm) | 1.09 | 1.02 | 1.07 | 1.02 | 1.06 | 1.00 |

| Aperture size (mm) | F7 (%) | F8 (%) | F9 (%) | F10 (%) | F11 (%) |
|---|---|---|---|---|---|
| 1.25 | 0.74 | 1.02 | 0.50 | 3.31 | 0.34 |
| 1.00 | 3.09 | 5.12 | 1.94 | 74.29 | 9.50 |
| 0.80 | 17.22 | 21.71 | 6.86 | 16.82 | 2.61 |
| 0.63 | 25.26 | 24.85 | 15.58 | 3.16 | 28.35 |
| 0.40 | 53.27 | 46.24 | 70.77 | 1.94 | 58.08 |
| Powder mass | 0.42 | 1.31 | 4.36 | 0.48 | 10.12 |
| Median (mm) | 0.46 | 0.49 | 0.37 | 0.98 | 0.42 |

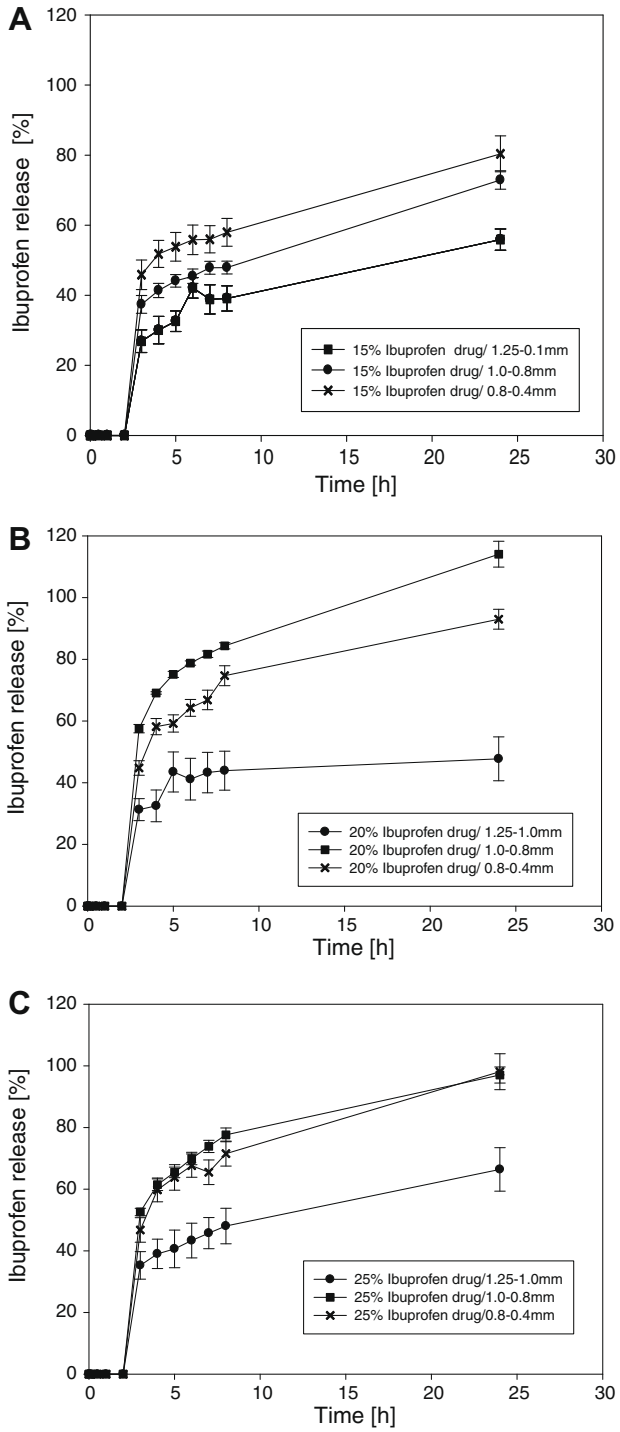


**Fig. 1.** Release profile depending on particle size and drug content: (A) 15% ibuprofen, (B) 20% ibuprofen and (C) 25% ibuprofen content in calcium stearate. Mean values ±SD. $n = 6$.

ing the first 2 h of the acidic phase in the pH shift dissolution test. After the phosphate buffer was added, between 27% and 45% of ibuprofen was released immediately after one hour which could be explained as initial drug dissolution. Furthermore, 39–57% ibuprofen was released after eight hours and approximately 70% was reached as highest value after 24 h.

As expected, the results demonstrated that the dissolution profile was highly affected by the particle size. The drug released increased with decreasing particle size. In all cases, the highest release with the 0.8–1 mm pellet fraction and the lowest release with the 1–1.25 mm fraction (see Fig. 1) were observed. In most cases, no important differences were found by comparing the 0.8–1 mm fraction with the smallest pellets ranging from 0.4 to 0.8 mm. However, it occurred only in the case of 20% ibuprofen pellets that the smallest pellet fraction did not show the highest release after 24 h.

In addition, the highest release as a function of the total drug content was studied. Ibuprofen, which sparingly dissolves in water, is soluble in ethanol with a solubility of 667 g/l ethanol. Pellets with 20% and 25% ibuprofen showed a significantly higher release in comparison with pellets with 15% drug content. This observation can be explained by the solubility of the drug and by the transport of ibuprofen towards the outer surface of the pellets (during the drying process) where it re-crystallised and formed solid bridges. The higher the drug content of the lipid matrix the more ibuprofen could be dissolved due to an improved water flux into the lipid matrix. Additionally, pellets prepared with higher ibuprofen contents were expected to have more active pharmaceutical ingredient close to the surface.

With 20% and 25% drug content, the pellets in the size range from 1 to 0.8 mm released almost 100% ibuprofen after 24 h.

As mentioned earlier, almost zero-order release kinetics could be achieved between 5 and 24 h, after the initial dose was released. Fig. 3 shows the release constants and regression coefficients. The mechanism of such a release profile may be explained by the unique pellet structure which did not release the drug within the first 2 h because of the limited solubility of ibuprofen in the acidic medium. Later, from 3 h to 5 h, the drug dissolved and defined pores formed on the pellet surface. Due to the water influx, a saturated drug solution exists inside the pellet. Since only 20% of the drug was incorporated, it can be assumed that pore structure and size became constant after 5 h. Furthermore, the pellets did not swell and the surface area was kept constant. Sink conditions were applied during all dissolution experiments.

In a second set of experiments, the influence of the ethanol concentration (used as granulation liquid) on the drug release was investigated. The granulation process which involves the evaporative removal of organic solvents has been further complicated by the introduction of stringent environmental regulations, controlling the use of organic solvents. Therefore, the ethanol content in the granulation liquid was decreased.

Preliminary experiments showed that by using only a pure aqueous system (i.e., without ethanol), no sufficient wetting of the powder mass could be achieved. This can be explained by the fact that calcium stearate showed no emulsifying properties and that the drug content, incorporated into the pellet mass, was too low to change the lipophilicity. From these preliminary studies (data not shown), 50% ethanol and 96% ethanol were defined as granulation liquids. Again as discussed before, the particle size influenced the release kinetic significantly. The data shown in Fig. 2 demonstrated also for 50% ethanol granulation liquid a higher release with the smaller pellet fraction. However, as shown in Fig. 3, 50% ethanol resulted in a general decrease in the ibuprofen release in comparison with 96% ethanol. This observation can be explained by the higher compression force during the extrusion/spheronisation process. The SEM pictures (Fig. 4) illustrated that the internal structure of the pellets showed a greater densification when produced with 50% ethanol. Therefore, the drug dissolution from the lipophilic matrix was more retarded in comparison with the pellets produced with 96% ethanol. The tensile strength of the pellets decreased significantly with decreasing ethanol content (96% ethanol: 0.728 MPa, ±0.228 SD; 50% ethanol: 0.272 MPa, ±0.092 SD, $p < 0.05$) and showed no influence on the release profile.

Due to the lower content of organic solvent and the lower drug release of the smallest pellet fraction, micropellets produced with 20% drug content and 80% CS and granulated with 50% ethanol

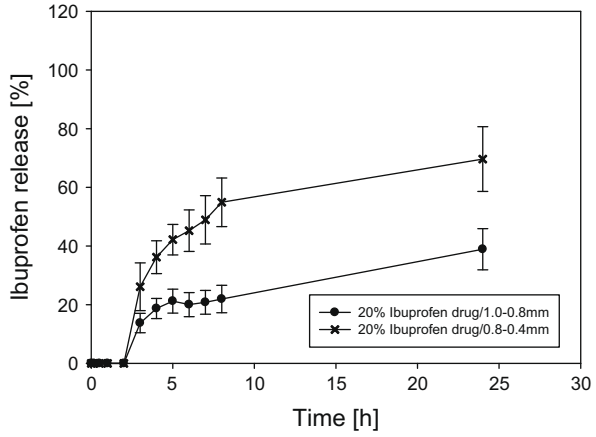


**Fig. 2.** Release profile of pellets prepared with 50% ethanol as granulation liquid. Mean values ±SD. $n = 6$.

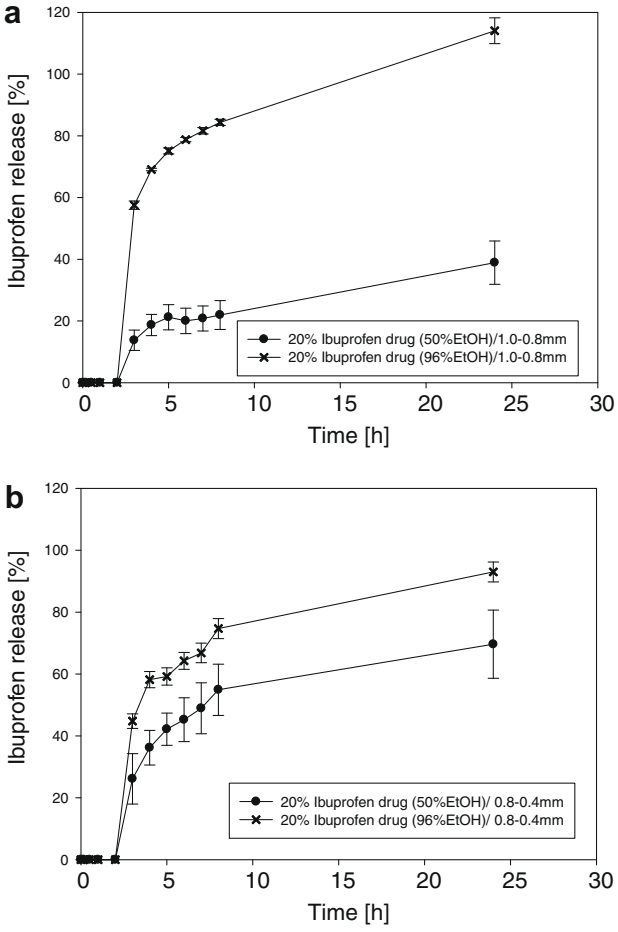


**Fig. 3.** Comparison of release profiles from pellets prepared with different ethanol concentrations of the granulation liquid and calculation of zero-order release between 5 and 24 h: (A) size yield of 1.0–0.8 mm, 50% EtOH: $k_{rel} = 1.09\%\ h^{-1}$ and $r^2 = 0.993$; 96% EtOH: $k_{rel} = 1.97\%\ h^{-1}$ and $r^2 = 0.984$; (B) size yield of 0.8–0.4 mm, 50% EtOH: $k_{rel} = 1.31\%\ h^{-1}$ and $r^2 = 0.913$; 96% EtOH: $k_{rel} = 1.60\%\ h^{-1}$ and $r^2 = 0.905$.

were further characterised in more detail from a technological point of view.

### 3.3. Mechanical properties

Pycnometric density, mercury porosimetry and the tensile strength were used to characterise the mechanical properties

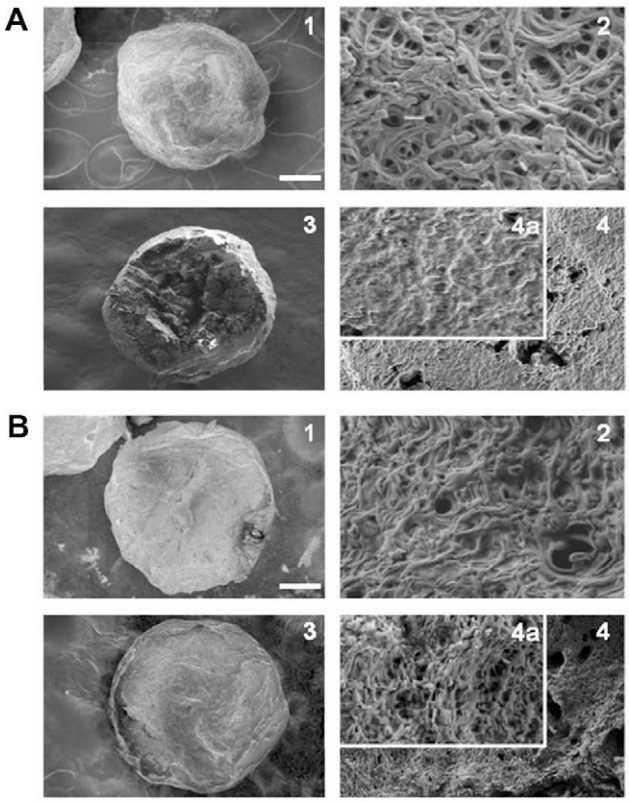


**Fig. 4.** Scanning electron microscopy images (A) of a 20% ibuprofen/CS pellet granulated with 50% ethanol, (A1) surface, bar size 200 μm, (A2) detailed surface structure, (A3) Cross cut, (A4) internal structure, (A4a) detailed internal structure; (B) of a 20% ibuprofen/CS pellet granulated with 96% ethanol, (B1) Surface, bar size 200 μm, (B2) detailed surface structure, (B3) cross cut, (B4) internal structure, (B4a) detailed internal structure.

**Table 5**
Porosity and density measurement of CS/drug pellets (F10).

| Helium density ($g/cm^3$) | Particle density ($g/cm^3$) | Pore volume ($cm^3/g$) | Mean pore diameter (μm) | Porosity (%) |
|---|---|---|---|---|
| 1.066 ± 0.0012 SD | 0.813 ± 0.00071 SD | 0.292 | 0.22 | 23.7 ± 0.021 SD |

of the pellets. Lipid pellets with low mechanical stability are unsuitable not only for the solid drug formulations but also for the incorporation into an aqueous suspension. To investigate the tensile strength and mean diameter, a rotational plate–plate rheometer was used to detect the compression force. However, the mean tensile strength, as mentioned before, was 0.272 MPa (±0.092 S.D.), and no hardening of the pellets was observed after storage. Pellets tested showed a mean diameter of 898.6 μm (±55.4 S.D.), implying that the breaking behaviour of the extrudate was homogenous and resulted in small spherical pellets after spheronisation.

From the porosimetry measurements, a porosity of 23.7% could be determined (Table 5). Thus, pellets based on CS and produced by the wet extrusion/spheronisation technique at a temperature of 20–25 °C showed low porosity and a slow drug release. They did not disintegrate during the in vitro release studies within 24 h.

It could be demonstrated that the wet lipid extrusion and spheronisation is a suitable method for the production of pellets consisting of calcium stearate as binder.

## 4. Conclusions

It was shown that among five lipids, vegetable calcium stearate was most suitable as a lipophilic pelletisation aid for the wet extrusion/spheronisation technique. Pellets with a spherical shape ($AR \leqslant 1.2$) were obtained in all calcium stearate formulations. The prolonged release profile was achieved in ibuprofen concentrations of 15–25% without any coating process. As expected, it was observed that the dissolution profile was highly affected by the particle size, as well as by the granulation liquid used for the experiments. The higher the drug content of the lipid matrix, the more ibuprofen was dissolved due to an improved water flux into the lipid pellet. Pellets produced with 50% ethanol resulted in a general decrease in ibuprofen release in comparison with pellets produced with 96% ethanol. Due to the greater densification of the pellets produced with 50% ethanol and due to the poor solubility of the drug in 50% ethanol, ibuprofen release from the CS matrix was more retarded. The tensile strength showed no influence on the release kinetic.

Spherical pellets with a high yield were obtained and did not disintegrate during the in vitro release studies within 24 h.

## Acknowledgements

The authors are grateful to G.L. Pharma GesmbH (Lannach, Austria) for supplying ibuprofen, Werba-Chem (Vienna, Austria) for supplying calcium stearate vegetable. The authors also thank Mrs. B. Berger from Anton Paar GmbH Graz, Austria for her assistance with the rotational plate–plate rheometer and Dr. J. Wagner, FELMI, Graz, Austria for his assistance with electron microscopy imaging.

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