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**THE USE OF PARTIALLY HYDROLYSED POLYVINYL ALCOHOL FOR THE PRODUCTION OF HIGH
DRUG-LOADED SUSTAINED RELEASE PELLETS VIA EXTRUSION-SPHERONISATION AND
COATING: IN VITRO AND IN VIVO EVALUATION**

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ABSTRACT

Partially hydrolysed polyvinyl alcohol (PVA) was evaluated as a pelletisation aid for the production of pellets with a high acetaminophen and metformin hydrochloride concentration (>70%, w/w). Mixtures with varying drug concentration and PVA/microcrystalline cellulose (MCC) ratios were processed via extrusion-spheronisation, either after addition of PVA as a dry powder or as an aqueous solution. Finally, high drug- loaded metformin pellets were coated with a methacrylic acid copolymer (Eudragit™ NM 30D) and evaluated for their sustained release potency *in vitro* and *in vivo*. The plasticity index of the wet mass increased by the addition of PVA to the formulation, which resulted in enhanced extrusion-spheronisation properties, even at a high drug load. Although the MCC concentration was successfully lowered by adding PVA, the inclusion of MCC in the formulation was essential to overcome problems related to the tackiness effect of PVA during extrusion. Overall, wet addition of PVA was superior to dry addition, as pellets with a higher mechanical strength and narrower particle size distribution were obtained. Pellets containing 87% (w/w) metformin hydrochloride were successfully layered with 20% (w/w) coating material, yielding sustained release pellets with a final drug load of 70% (w/w). In addition, the sustained release characteristics of the PVA-based pellets with a high drug content were confirmed *in vivo* as no difference with the Glucophage™ SR reference formulation was observed.

KEYWORDS: extrusion-spheronisation, pelletisation aid, polyvinyl alcohol, high drug load, pellets, sustained release

INTRODUCTION

Multiparticulate drug delivery systems (e.g. pellets) are important for therapeutic applications due to their distinct advantages compared to single-unit systems such as reproducible gastrointestinal transit time, flexibility to blend pellets with different release patterns (personalized medicines) and low risk of dose dumping. [1] Pellets, which for pharmaceutical applications are defined as small (between 0.5 and 2.0 mm), free-flowing, spherical particles, can be obtained by solution or suspension layering of cores, powder layering, spray congealing, melt spheronisation or extrusion-spheronisation. [2] The latter is the best option to produce pellets with high drug load. However, this technique requires specific properties of the formulation during the different steps of the process: (a) a cohesive wet mass which does not adhere to the extruder or spheroniser, and retains some degree of rigidity; (b) the extrudates need to be brittle enough to break into smaller extrudates and have some degree of plasticity to deform into spheres. [3] Although high drug loaded pellet formulations (e.g. 90% w/w of 5-ASA) have been reported in literature [4], most drug molecules do not exhibit the required characteristics for extrusion/spheronization and microcrystalline cellulose (MCC) is conventionally included as excipient to obtain formulations with sufficient rigidity, plasticity and water absorbing capacity. This often limits the drug load in MCC-based pellets, which restricts the use of extrusion/spheronisation for the manufacturing of high drug-loaded formulations. [5] Therefore, several alternatives such as biopolymers (e.g. starch, chitosan, carrageenan) or synthetic polymers (e.g. hydroxy-propylmethylcellulose, polyethylene oxide) are proposed in order to reduce the MCC concentration in the pellets. However, these materials have inferior properties (e.g., less water holding capacity, ionic polymers require granulation liquid with a specific pH) for extrusion-spheronisation, compared to MCC. [6] In this study, partially hydrolysed polyvinyl alcohol (PVA) was evaluated as a pelletisation aid for the manufacturing of high drug-loaded pellets via extrusion-spheronisation. To investigate the impact of PVA on pellet quality, different acetaminophen concentrations were processed in combination with varying PVA/MCC ratios. PVA was added as a dry powder or as an aqueous solution and its impact on the plasticity (i.e. the property of a material which allows it to be repeatedly deformed without rupture when acted upon by a force sufficient to cause deformation and which allows it to retain its shape after the applied force has been removed) of the wet mass was quantified. [7] After extrusion-spheronisation, all pellet formulations were characterized (aspect ratio (AR), sphericity, particle size distribution (PSD) and friability)

96 and compared to MCC pellets as a reference. As the processability of the wet mass might be
97 affected by the API solubility, the same experiments were conducted with metformin.HCl. [2]
98 The aqueous solubility (at 25 °C) of acetaminophen and metformin hydrochloride are 14 and
99 50 g/L, respectively. [8][9] Varying coating levels were applied to the pellets containing the
100 highest metformin.HCl concentration and with the lowest friability. After curing, *in vitro*
101 release kinetics were evaluated as a function of coating thickness. Finally, *in vivo* performance
102 of the most promising sustained release metformin hydrochloride pellets was investigated in
103 dogs and compared to a commercially available reference formulation (GlucophageTM SR 500
104 mg).

MATERIALS AND METHODS

2.1 Materials

Pharmaceutical grade polyvinylalcohol (PVA₄₋₈₈, 88% hydrolysed, obtained from Merck, Darmstadt, Germany), and microcrystalline cellulose (MCC, Avicel® PH101, FMC Wallingstown, Little Island, Cork, Ireland) were used as pelletisation aids. Micronized acetaminophen (Atabay, Istanbul, Turkey) and metformin.HCl (Granules, Jeedimetla, India) were used as model drugs. A more detailed description of the particle size and geometry of the raw materials was listed in **Table 1**. Demineralized water or an aqueous solution of PVA was used as granulation liquid.

For coating trials, a methacrylic acid copolymer (Eudragit™ NM 30D) and hydroxypropylmethylcellulose (Methocel™ E5) were supplied by Evonik (Darmstadt, Germany) and The Dow Chemical Company (Midland, Michigan, USA), respectively. Talc and polysorbate 80 (Tween 80™) were obtained from Fagron (Waregem, Belgium).

2.2 Plasticity measurements: Atterberg limits

An ASTM standard test (ASTM D 4318) was used to quantify the liquid limit, plastic limit and plasticity index of the wet mass. The plasticity index was defined as the range of water content over which a wet mass behaves plastically. Mathematically, it was calculated as the difference between the liquid limit and the plastic limit. The liquid limit was determined by spreading an amount of the wet mass in a brass cup. A grooving tool was then used to divide the material into two symmetrical halves separated by 13 mm. By repeatedly dropping the cup in a mechanical device, both halves were able to flow towards the centre of the cup and make contact at the bottom of the groove. As the multipoint liquid limit (i.e. method A of ASTM D 4318) was used, four trials over a wide range of water contents were performed. The number of drops required before both halves made contact with each other was plotted as a function of water content on a semi-logarithmic graph, with the water content as ordinates on the arithmetical scale, and the number of drops as abscissas on a logarithmic scale. Subsequently, the best fit line was plotted. The water content corresponding to the intersection of the line with the 25-drop abscissa was taken as the liquid limit of the wet mass. To determine the water content from each trial, a standard ASTM test (ASTM D 2216) was used. Therefore, initial masses (container plus wet mass) were recorded immediately and after 24 h oven drying at 105 °C. The plastic limit was determined by alternately pressing and rolling a small amount

(± 12 g) of wet masses with different water content into a 3.2 mm diameter thread. The water content at which the thread crumbled and could no longer be pressed together and re-rolled was reported as the plastic limit. All experiments were performed in triplicate.

2.3 Preparation of drug-loaded pellets

The active pharmaceutical ingredient (API) and Avicel® PH101 (with or without the addition of PVA) were dry mixed in different ratios (**Table 2**) during 5 min in a planetary mixer (Kenwood Chief, Hampshire, UK), using a K-shaped mixing arm. The required amount of demineralized water or aqueous PVA solution was gradually added to the powder mixture. After 10 min of mixing, the wet mass was extruded at an extrusion speed of 100 rpm using a single screw extruder (Dome extruder DG-L1, Fuji Paudal, Tokyo, Japan) equipped with a dome-shaped extrusion screen having a thickness of 1.2 mm and 33 1mm-perforations per cm². The resulting extrudates were spheronized for 1 min at a speed of 1000 rpm using a spheroniser having a cross-hatched geometry friction plate (Caleva Model 15, Caleva, Sturminster Newton, Dorset, UK) with a diameter of 38 cm. The features on the friction plate had a size of 6.5 mm and were positioned at a distance of 3.5 mm of each other. The pellets were oven dried for 24 h at 40 °C. Each batch of pellets was sieved for 5 min at 2 mm amplitude using a sieve shaker (Retsch, Haan, Germany) to isolate the 850-1120 μ m size fraction.

2.4 Preparation of sustained release pellets by coating

The coating suspension (batch size 1 kg) was prepared in four steps: (1) 10 g of HPMC was added to 559.7 g demineralized water. Subsequently, the mixture was heated to 55 °C and mixed using a high speed mixer (Silverson™ L4R, Silverson Machines, Waterside, Chesham, Bucks, England) until a clear solution was obtained; (2) 30.3 g of a 33% aqueous solution of polysorbate 80 and 100 g talc were added and dispersed for at least 10 min; (3) the resulting excipient suspension was slowly poured into 300 g Eudragit™ NM 30D with a magnetic stirrer at room temperature for 5 min; (4) the spray suspension was passed through a 0.5 mm sieve and was then continuously stirred with a magnetic stirrer at room temperature during coating experiments.

Varying coating levels (0, 8, 14 and 20%, w/w) were applied to pellets containing 87.3% (w/w) metformin.HCl (F20 in Table 5, sieve fraction 850-1120 μ m). All experiments were performed

using a laboratory scale fluid bed granulator (GPCG 1, Glatt, Binzen, Germany). The spray suspension was added at a flow rate of 1.85 mL/min through a 0.8 mm nozzle (bottom spray). The atomizing pressure and inlet air temperature were set at 2 bar and 40 °C, respectively. The resulting outlet air temperature and product temperature were between 20 and 25 °C. An inlet air velocity of 5 m/s was used and the filter bags were shaken every 15 s for a period of 5 s. All coated pellets were cured in an oven at 40 °C for 24 h. An overview of their final composition is listed in **Table 6**.

2.5 Pellet characterization

2.5.1 Pellet size and shape

The size and shape of the pellets were determined using dynamic image analysis (QicPic, Clausthal- Zellerfeld, Germany). D_{10} and D_{90} , which are the respective particle sizes (in μm) at 10 and 90% cumulative undersize, were determined. The width of the PSD was determined by calculating the span. [10]

$$\text{Span} = D_{90} - D_{10}$$

An independent sample t-test was performed with SPSS Statistics 23 (IBM, New York, United States) to detect significant differences between span values. The shape of the pellets was expressed as aspect ratio (AR) and sphericity. AR was defined as the ratio of the maximal Feret diameter ($Feret_{max}$) and minimal Feret diameter ($Feret_{min}$, measured at an angle of 90° to $Feret_{max}$).

$$AR = \frac{Feret_{max}}{Feret_{min}}$$

Sphericity was defined as the ratio between the perimeter of a circle that has the same projected area (A) as the particle (P_{EQPC}) to the measured perimeter (P_{REAL}), and is a value between 0 and 1. [11]

$$\text{Sphericity} = \frac{P_{EQPC}}{P_{REAL}} = \frac{2\sqrt{\pi A}}{P_{REAL}}$$

All formulations were measured in triplicate (± 10 g for each sample).

2.5.2 Loss on drying

After drying, the residual moisture content of the pellets was analysed by loss on drying (LOD) using a Mettler LP16 moisture analyser, including an infrared dryer and a Mettler PM460 balance (Mettler-Toledo, Zaventem, Belgium). A sample of approximately 2 g was dried at 105 °C until the rate of change was less than 0.1% LOD per 30 s. The measurements were performed in triplicate.

2.5.3 Friability

Pellet friability was determined using a friabilator equipped with an abrasion drum (Pharma Test, Hainburg, Germany). Approximately 10 g pellets within the size range of 850-1120 µm were weighed and added to the abrasion drum together with 200 glass beads (4 mm in diameter). The abrasion drum was rotated at 25 rpm for 10 min. At the end of the run, the content of the abrasion drum was sieved using a 850 µm sieve and the fraction below 850 µm was weighed. Friability was measured in triplicate and calculated as follows:

$$Friability (\%) = \frac{Fraction < 850 \mu m (g)}{Total sample (g)}$$

2.5.4 Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was used to determine differences in pellet surface morphology between the coated and uncoated pellets (before and after *in vitro* dissolution testing). Prior to imaging, samples were coated with a thin gold layer. SEM images were recorded using a tabletop SEM (PHENOM™, FEI Company).

2.6 In vitro dissolution

Drug release from (un)coated metformin hydrochloride pellets was determined using the paddle method on a VK 7010 dissolution system (VanKel Industries, New Jersey, USA) at a speed of 100 rpm. An amount of pellets corresponding to 250 mg metformin.HCl was placed in 900 mL 0.1 N HCl (pH 1.2) or phosphate buffer solution (pH 6.8), set at a temperature of 37 ± 0.5 °C. Samples were withdrawn at 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h, and spectrophotometrically (UV-1650PC, Shimadzu Benelux, Antwerp, Belgium) analysed using a wavelength of 232 nm.

2.7 In vivo

The bioavailability study (application ECD 2013/127) was approved by the Ethical Committee of the Faculty of Veterinary Medicine (Ghent University).

2.7.1 Animal study

In vivo experiments were performed using the most promising sustained release pellet formulation (i.e. F24) and a reference formulation (Glucophage™ SR 500 mg, ½ tablet). Open label cross-over assays were performed on 6 male beagle dogs (10-13 kg) with a wash-out period of at least 8 days. The pellet and reference formulations were orally administered to fasted dogs (no food intake was allowed 12 h prior to drug administration) with 20 mL water. During the experiment the dogs were only allowed to drink water. Blood samples were collected after 1, 2, 3, 4, 5, 6, 8 and 12 h post administration, and were stored at -25 °C until analysis.

2.7.2 Metformin assay

An extraction method developed by *Gabr et al.* was optimized. [12] After de-freezing, plasma samples were centrifuged using a Centric 322A (Tehtnica, Slovenia) at 2300 g for 10 min. 280 µL of the supernatant was spiked with 20 µL 0.05 mg/mL ranitidine solution. During a first extraction step, 50 µL 10 M sodium hydroxide solution and 3 mL organic phase (1-butanol/hexane, 50/50, v/v) were added. The tubes were mixed using a Turbula™ mixer (Willy A. Bachofen Maschinenfabrik, Switzerland) for 30 min at an intensity of 79 rpm. After centrifugation the upper organic layer was transferred to a clean test tube. Back extraction was performed by adding 1 mL 2M HCl, mixing the tubes (79 rpm, 10 min) and centrifugation (10 min, 2300 g). Afterwards the organic layer was removed, and 400 µL sodium hydroxide (10 M) and 2 mL organic phase (1-butanol/hexane, 50/50, v/v) were added. After mixing (79 rpm, 30 min) and centrifugation (10 min, 2300 g) the organic layer was transferred into a clean glass tube and evaporated to dryness under a nitrogen stream.

The HPLC system (Merck-Hitachi, Darmstadt, Germany) consisted of an isocratic solvent pump (L-7100) set at a constant flow rate of 0.7 mL/min, an auto-sampler injection system (L-7200) with a 100 µL loop (Valco Instruments Corporation, Houston, Texas, USA), a reversed-phase column and pre-column (LiChroCart® 250-4 and LiChrospher® 100RP-18 5 µm, respectively) and a variable wavelength UV-detector (L-7400) set at 236 nm. The mobile phase composition

remained constant over time and consisted of potassium dihydrogen phosphate buffer (adjusted to pH 6.5 with 2 M NaOH)/acetonitrile (66/34, v/v) and 3 mM sodium dodecyl sulphate (SDS).

2.7.3 Data analysis

Peak integration was performed using the software package D-7000 HSM Chromatography Data Manager. The peak plasma concentration ($C_{\max}$), time to reach $C_{\max}$ ($T_{\max}$), half value duration ($HVD_{t50\%C_{\max}}$) and area under the curve (AUC_{0-12h}) were calculated using a commercial software package (MATLAB 8.6, The MathWorks, Natick, USA, 2015). The sustained-release characteristics of the formulation were evaluated by calculating the R_D ratio between the $HVD_{t50\%C_{\max}}$ values of a test formulation and an immediate-release formulation. A ratio of 1.5, 2 and >3 indicates low, intermediate and strong sustained release characteristics, respectively. A $HVD_{t50\%C_{\max}}$ value of 3.2 h for immediate release metformin tablets, administered to beagle dogs, was abstracted from literature and used to calculate the R_D ratio. [13][14][15] R_D values should be interpreted with caution as the $HVD_{t50\%C_{\max}}$ from the immediate release formulation was determined from another *in vivo* study.

2.7.4 Statistical analysis

The effect of metformin.HCl formulation on the bioavailability was assessed using an independent sample t-test. The normality of the residuals was evaluated with a Kolmogorov-Smirnov test. To test the assumption of variance homogeneity, a Levene's test was used. The statistical analysis was performed using SPSS (IBM SPSS Statistics for Windows, version 23.0, Armonk, New York, USA, 2015).

RESULTS AND DISCUSSION

When processing mixtures of API (acetaminophen or metformin.HCl) and MCC via extrusion-spheronisation, the drug load was limited to 50% (w/w) as the process yield as well as the pellet properties (shape, size) were negatively affected when the MCC fraction in the formulation was decreased. Since wetted MCC acts like a 'molecular sponge' that has the proper rheological properties, cohesiveness and plasticity to yield strong and spherical particles via extrusion-spheronisation, the MCC content of these mixtures was too low to yield acceptable pellets with a sufficient mechanical integrity at high drug load. [16][17] Therefore, PVA was added as pelletisation aid to MCC-based formulations as an excipient which improved the plasticity of the MCC formulations with a high drug content (**Table 2**). Using a standard test for measuring the plasticity index of soil (i.e. the Atterberg method, ASTM D 4318) the impact of PVA addition on the plasticity of the wet mass was determined. Whereas an increase of drug content in MCC formulations was correlated with a drop of the plasticity index (20.7 for a 50/50 API/MCC mixture vs. 4.8 and 8.9 for formulations containing 80% paracetamol and 90% metformin, respectively), the addition of PVA significantly improved the plasticity of the wet mass which is a crucial factor during an extrusion-spheronisation process (**Table 3**). To assess the impact of PVA addition and its effect on the plasticity during processing of the formulation via extrusion-spheronisation, formulations with different acetaminophen concentrations (70-90%, w/w) were processed in combination with varying PVA content. The PVA/MCC ratios tested were the same for formulations with different API content (0/100, 5/95, 10/90, 20/80 and 50/50). Whereas high drug-loaded formulations without the addition of PVA (i.e. F1, F6 and F11 in Table 2) could not be processed via extrusion-spheronisation due to shark skinning and the high brittleness of the extrudates during spheronisation, the addition of a low PVA concentration improved the extrusion properties of the formulations, yielding extrudates with a smooth surface, even for formulations with a low MCC content, e.g. F14 containing 90% acetaminophen and only 8% MCC. In contrast, adding an excess of PVA to the formulation (i.e. F5, F10 and F15 with a 50/50 PVA/MCC ratio) yielded sticky extrudates that were not suitable for spheronisation, indicating that successful extrusion-spheronisation was only possible if a certain MCC/PVA ratio (corresponding to a specific plasticity range of the wetted formulation) was used. Moreover, one can assume that the inclusion of MCC in the formulation was essential to overcome the tackiness of PVA. Besides the MCC/PVA ratio, the processing of the wet mass also depended on the PVA addition method to the formulation.

While all formulations could be processed after dry addition of PVA, the wet addition method could not be universally applied: in case of formulations with a higher PVA content the PVA concentration in the granulation liquid was too high, resulting in a too viscous granulation liquid (e.g. F5). The addition of PVA to the formulation also impacted the water content required for efficient extrusion-spheronisation: less water was needed to process formulations with a higher PVA/MCC ratio. This phenomenon was linked to the lower MCC concentration (which has a large water-holding capacity) and the higher PVA concentration (which becomes tacky when wetted) in these samples.

Immediately after extrusion, all rigid and non-sticky extrudates (i.e. F2, F3, F4, F7, F8, F9, F14 and F15) were spheronized. To investigate the impact of drug load and MCC/PVA ratio on pellet quality, the particle size distribution, morphology and friability of the different pellet formulations was compared with pure MCC pellets (F16). Overall the pellet size of PVA-containing formulations was higher compared to the reference, as shown in **Fig. 1**. During extrusion it was observed that extrudates containing PVA were less brittle compared to MCC extrudates. Hence, the PVA-containing extrudates broke into longer segments during spheronisation, yielding larger pellets. The method of PVA addition also affected the size distribution of the pellets. In general, addition of PVA as an aqueous solution significantly ($p < 0.05$) reduced span values (**Table 4**). A phenomenon that was already reported by Chatlapalli et al. and might be attributed to the better distribution of the binder at the molecular level. [18] Moreover, lower span values were found when a higher PVA/MCC ratio was used. However, it was observed that increasing the drug load from 70% to 90% (hence lowering the amount of PVA and MCC in the pellets) resulted in higher span values. This indicated that PVA and MCC were essential to provide the wet mass with sufficient rigidity, plasticity and water absorbing capacity for the production of spheres with narrow PSD. [19] Overall, the span values of formulations containing PVA were higher.

Pellet morphology was measured in terms of AR and sphericity, whereby the MCC pellets were compared with PVA-containing formulations (fraction with a particle size between 850 and 1120 μm was used for all formulations). A mean AR lower or equal to 1.20 is considered as sufficient for pharmaceutical pellets. [20] Wet addition of PVA via an aqueous solution yielded a slightly lower AR (**Fig. 2**). However, it should be considered that all PVA formulations had a wider AR range. Due to the wider span of AR, it was hard to distinguish any influence of drug load or addition method of PVA. The mean sphericity (i.e. s50) of all PVA-formulations was

high (>0.85). The sphericity range (i.e. s90-s10) of the PVA formulations was higher than the MCC pellets. A phenomenon that was less pronounced when more PVA was added via the wet addition method. SEM photographs used to visualize the pellet surface morphology were in agreement with AR and sphericity data: round spheres with a smooth surface were observed, and the structure of PVA-based pellets was very similar to MCC pellets (**S.1.**).

The friability was determined to quantify the mechanical properties of the pellets as these must withstand mechanical stress during post-processing steps (e.g. coating, packaging). As presented in **Table 5**, the friability was slightly higher for pellets with a higher drug load, possibly due to the lower excipient concentration (i.e. PVA and MCC). Overall, wet addition of PVA as a binder in the formulation was the best option to yield pellets with a high mechanical strength. All pellets processed with a PVA solution had a friability below 1% for all drug loadings (70–90%). Dry addition of PVA, specifically at higher drug loads, resulted in pellets with a lower mechanical strength.

Usually, the drug load of sustained release pellets for highly water soluble drugs is limited as large amounts of MCC (to enable extrusion-spheronisation) and release retarding polymer are needed. [21] As the MCC concentration could be lowered by the addition of PVA, high quality pellets could be obtained with a metformin load up to 90%. Based on its high drug content and low friability ($0.66 \pm 0.03\%$), formulation 20 (F20) was selected for coating trials. Different coating levels were applied (**Table 6**) and the influence on drug release was plotted as a function of dissolution time. As shown in **Fig. 3. (A)**, release kinetics decreased in function of coating thickness. Moreover, it was found that at least 20% (w/w) coating (percentage based on pellet weight) was needed to sustain drug release for 12 h. Hu et al. already reported the burst-release of metformin.HCl sustained release pellets and attributed this finding to the high water solubility of the drug. [21] When coating experiments were performed with an aqueous solution, the drug on the pellet surface dissolved fast. Therefore, it was able to diffuse into the polymer film during coating trials and act as a pore-forming agent during dissolution testing. A phenomenon that could only be countered by using sufficient coating material (>20%) or by pre-treating the pellets with talc. The influence of dissolution testing on pellet morphology (i.e. surface porosity) was examined via SEM on coated and uncoated pellets (**S. 1.**). Whereas the surface porosity of the uncoated pellets increased after 12 h dissolution testing, the morphology of the 20% coated pellets remained unchanged, further confirming the need of sufficient coating material to avoid burst-phenomena. For the

377 GlucophageTM SR tablet, a gel-like layer was formed around the matrix tablet due to the
378 hydration of hydroxypropylmethylcellulose and sodium carboxymethylcellulose which are
379 incorporated as release retarding agents. [22]

380 The *in vivo* pharmacokinetic behavior of the most promising coated pellet formulation (F24)
381 was investigated and compared to the commercially available GlucophageTM SR 500 mg
382 reference formulation (**Fig. 3. (B) and Table 7**). For the pellet formulation, a maximum plasma
383 level of 2.5 µg/mL was reached 3.5 h (T_{max}) post administration. In case of GlucophageTM SR
384 ($\frac{1}{2}$ tablet), a C_{max} value of 2.4 µg /mL was observed 2.8 h (T_{max}) after oral intake. The
385 $HVD_{T50\%C_{max}}$ values were 5.1 and 5.6 h, resulting in R_D values of 1.6 and 1.7 for the pellets and
386 GlucophageTM SR reference formulations, respectively. Despite the narrow absorption range
387 (i.e. mainly upper part of gastro-intestinal tract) of metformin hydrochloride and shorter
388 gastro-intestinal residence time of multiparticulate dosage forms, the pellet and tablet
389 formulations did not have significantly different pharmacokinetic parameters (i.e. AUC, T_{max} ,
390 C_{max} , $HVD_{T50\%C_{max}}$ and R_D). [23] An observation that could be explained by the higher sensitivity
391 of the hydrated gel layer (at the surface of the Glucophage tablets) to gastrointestinal shear
392 forces. [24][25][26] This hypothesis was confirmed after *in vivo* experiments as no residue of
393 the reference tablet could be detected in the faeces. [27] In contrast, the geometric shape of
394 the pellets (which had no residual drug content) was unaffected.

CONCLUSIONS

This study demonstrated that PVA is a promising pelletisation aid as it affects the plasticity of the wet powder mass during extrusion-spheronisation. Via the incorporation of a low content of PVA, formulations containing up to 90% (w/w) drug could be processed via extrusion-spheronisation, despite their low MCC content. The enhanced extrusion-spheronisation properties of the PVA-containing mixtures was linked to the plasticity index. PVA pellets were successfully coated with an acrylic-based sustained release polymer, sustaining drug release from pellets containing 70% (w/w) metformin hydrochloride over a period of 12 h. After oral administration the *in vivo* performance of the coated pellets did not significantly differ from the the commercially available GlucophageTM SR reference formulation.

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Figures

Fig. 1. Particle size distributions (mean $\pm$ SD, n=3) of formulations containing 70% drug (Form. 2 (o), 3 ($\square$), 4 (Δ)), 80% drug (Form. 7 (o), 8 ($\square$), 9 (Δ)) or 90% drug (Form. 14 (o), 15 ($\square$)) and PVA added dry (black closed symbol) or wet (blue open symbol). Microcrystalline cellulose pellets were used as reference (X).

488 **Fig. 2.** Aspect ratio and sphericity (mean $\pm$ SD, n=3) of formulations as a function of particle
489 size (D10, D50 and D90), PVA/MCC ratio (5/95 – 20/80%) and drug load (70-90%). PVA was
490 added either dry (d) or wet (w). MCC pellets without drug were used as reference (Ref.). Sieve
491 fraction 710-1000 μm was used (n=3).

492 **Fig. 3. (A)** Mean *in vitro* dissolution profiles ($\pm$ SD, n=3) of metformin.HCl pellets with different
493 coating levels (($\square$) 0, (Δ) 8, (∇) 14 and ($\bullet$) 20% (w/w)) and (*) GlucophageTM SR 500 (1/2 tablet)
494 reference. **(B)** Mean plasma concentration-time profiles ($\pm$ SD, n=6) after oral administration
495 of 250 mg Metformin.HCl to beagle dogs: ($\bullet$) coated PVA pellets (F24) and (*) GlucophageTM
496 SR 500 (1/2 tablet).

Tables

Table 1. Powder characteristics of raw materials.

	D10 (µm)	D50 (µm)	D90 (µm)	Aspect ratio	Sphericity
Acetaminophen	1.7	6.4	20.1	0.58	0.84
Metformin.HCl	8.4	51.6	150.2	0.66	0.87
MCC	19.8	54.1	113.1	0.53	0.76

Table 2. Composition of the pellet formulations processed via extrusion-spheronisation.

Form.	Concentration (%)			Ratio (PVA/MCC)	Water content (%) [*]
	Acetaminophen	PVA	MCC		
F1	70	0	30	0/100	-
F2	70	1.5	28.5	5/95	53.3
F3	70	3	27	10/90	46.2
F4	70	6	24	20/80	38.3
F5	70	15	15	50/50	-
F6	80	0	20	0/100	-
F7	80	1	19	5/95	43.3
F8	80	2	18	10/90	40.6
F9	80	4	16	20/80	33.2
F10	80	10	10	50/50	22.9
F11	90	0	10	0/100	-
F12	90	0.5	9.5	5/95	36.3
F13	90	1	9	10/90	35.0
F14	90	2	8	20/80	30.2
F15	90	5	5	50/50	24.5
F16	-	-	100	-	120
F17	50	-	50	-	55.7
Form.	Metformin.HCl	PVA	MCC	Ratio (PVA/MCC)	Water content (%) [*]
F18	90	0	10	0/100	-
F19	88.7	1.5	9.8	13/87	18.5
F20	87.3	2.9	9.7	23/77	17.0

^{*}Water content was calculated as a percentage of the total dry weight of each formulation

504 **Table 3.** Plasticity indexes (mean $\pm$ SD, n=3) of the wet mass used for the manufacturing of
 505 different pellet formulations.

Concentration (%)				
Form.	Acetaminophen	PVA	MCC	Plasticity index (%)
F6	80	0	20	4.8 ± 1.3
F7	80	1	19	4.9 ± 0.4
F8	80	2	18	12.3 ± 3.0
F9	80	4	16	16.5 ± 0.1
F10	80	10	10	48.5 ± 1.3
F17	50	-	50	20.7 ± 3.0
Form.	Metformin.HCl	PVA	MCC	Plasticity index (%)
F18	90	0	10	8.9 ± 1.8
F20	87.3	3	9.7	17.9 ± 0.9

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Table 4. Span (D_{90} - D_{10} , μm) (mean $\pm$ SD, $n=3$) of several formulations as a function of acetaminophen concentration (70-90%), PVA/MCC cellulose ratio (0/100 – 50/50). PVA was added either as dry powder or aqueous dispersion. The significance of the results was determined with independent sample t-test. Span values in the same row with different superscripts are different at the 0.05 level of significance.

	Formulation	PVA method addition	
		Dry	Wet
70 %	F2	1486 $\pm$ 348 ^a	640 $\pm$ 23 ^b
	F3	1040 $\pm$ 85 ^a	679 $\pm$ 52 ^b
	F4	1158 $\pm$ 197 ^a	467 $\pm$ 32 ^b
80 %	F7	1198 $\pm$ 181 ^a	1114 $\pm$ 64 ^a
	F8	926 $\pm$ 42 ^a	998 $\pm$ 35 ^a
	F9	965 $\pm$ 68 ^a	803 $\pm$ 22 ^b
90 %	F14	1143 $\pm$ 198 ^a	1172 $\pm$ 355 ^a
	F15	2338 $\pm$ 253 ^a	805 $\pm$ 73 ^b
Ref.	F17	434 $\pm$ 19	

Table 5. Friability (%) (mean $\pm$ SD, $n=3$) of pellets (850-1120 μm) as a function of acetaminophen load and PVA/MCC ratio.

	Formulation	PVA method addition	
		Dry	Wet
70%	F2	0.10 $\pm$ 0.02	0.15 $\pm$ 0.01
	F3	0.39 $\pm$ 0.01	0.35 $\pm$ 0.02
	F4	0.18 $\pm$ 0.02	0.02 $\pm$ 0.01
80%	F7	0.41 $\pm$ 0.01	0.66 $\pm$ 0.03
	F8	1.12 $\pm$ 0.03	0.85 $\pm$ 0.04
	F9	1.50 $\pm$ 0.04	0.55 $\pm$ 0.01
	F10	0.40 $\pm$ 0.02	-
90%	F12	1.35 $\pm$ 0.16	-
	F13	1.36 $\pm$ 0.23	-
	F14	3.90 $\pm$ 0.20	0.35 $\pm$ 0.01
	F15	0.56 $\pm$ 0.07	0.17 $\pm$ 0.01

Table 6. Composition of coated metformin.HCl pellet formulations.

Form.	Concentration (%)			
	Metformin.HCl	PVA	MCC	Coating
F21	87.3	2.9	9.7	0.0
F22	80.4	2.7	8.9	7.9
F23	74.9	2.5	8.3	14.2
F24	69.5	2.3	7.7	20.4

Table 7. Mean pharmacokinetic parameters ($\pm$ SD, n=6) after oral administration of 250 mg metformin.HCl to dogs as pellets and Glucophage™ SR 500 (1/2 tablet).

Formulation	C _{max} (µg/mL)	T _{max} (h)	AUC _{0-12h} (µg.h/mL)	HVD _{t50%C_{max}} (h)	R _D
pellets	2.5 $\pm$ 0.2	3.5 $\pm$ 1.0	14.5 $\pm$ 2.4	5.1 $\pm$ 1.4	1.6 $\pm$ 0.4
Glucophage™ SR	2.4 $\pm$ 0.2	2.8 $\pm$ 0.4	15.0 $\pm$ 0.9	5.6 $\pm$ 0.6	1.7 $\pm$ 0.2

525 **Supplementary data**

526 **S. 1.** Scanning electron microscopy images of (A) uncoated (i.e. F20) and (B) coated PVA
527 pellet formulation (i.e. F24) before (top) and after (bottom) dissolution experiments.

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