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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.

1. 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 gastro-intestinal transit time, flexibility to blend pellets with different release patterns (personalized medicines) and low risk of dose dumping (Dukic-Ott et al., 2007). 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 (Lustig-Gustafsson et al., 1999). 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 (Swarbrick, 2006). Although high drug loaded pellet formulations (e.g. 90% w/w of 5-ASA) have been reported in literature (Di Pretero et al., 2010), 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

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(Mallipeddi et al., 2010). 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 (Dukic-Ott et al., 2009).

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 (Andrade et al., 2010). mAfter extrusion-spheronisation, all pellet formulations were characterized (aspect ratio (AR), sphericity, particle size distribution (PSD) and friability) and compared to MCC pellets as a reference. As the processability of the wet mass might be affected by the API solubility, the same experiments were conducted with metformin.HCl (Lustig-Gustafsson et al., 1999). The aqueous solubility (at 25 °C) of acetaminophen and metformin hydrochloride are 14 and 50 g/L, respectively (Anon., 2016a,c). Varying coating levels were applied to the pellets containing the highest metformin.HCl concentration and with the lowest friability. After curing, *in vitro* release kinetics were evaluated as a function of coating thickness. Finally, *in vivo* performance of the most promising sustained release metformin hydrochloride pellets was investigated in dogs and compared to a commercially available reference formulation (Glucophage™ SR 500 mg).

2. Materials and methods

2.1. Materials

Pharmaceutical grade polyvinylalcohol ($PVA_{4\text{-}88}$, 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).

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

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

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

	Concentration (%)				
Form.	Acetaminophen	PVA	MCC	Ratio (PVA/MCC)	Water content (%)[a]
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 (%)[a]
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

[a] Water content was calculated as a percentage of the total dry weight of each formulation.