

PECTINIC ACID, A NOVEL EXCIPIENT FOR PRODUCTION OF PELLETS

I.Tho¹, S.A.Sande¹ and P.Kleinebudde²

¹ Dept. of Pharmaceutics, School of Pharmacy, University of Oslo, Norway

² Institute of Pharmaceutics and Biopharmaceutics, Martin-Luther University Halle-Wittenberg, Germany

Introduction

Due to the unique pelletisation properties of microcrystalline cellulose (MCC), this has been the number one excipient for production of pellets with the extrusion/spheronisation technique. A disadvantage of MCC is that it does not disintegrate, and as a consequence especially low soluble drug substances are released slowly. Other excipients have therefore been studied as an alternative to MCC.

Pectin, a naturally occurring polysaccharide, has been one candidate. Different types of pectin (degree of methoxylation 35 – 72 %, and amid substitution) has previously been evaluated, but none of the types were capable of producing mechanically stable, spherical products with a purely aqueous granulation liquid [1].

The objective of this study was to investigate the ability of a pectin-derivative with a very low solubility in water for pellets production by extrusion/spheronisation.

Experimental methods

• Materials

Formulations containing pectinic acid with a DM of 4 % (type 049/01, Herbstreith & Fox GmbH, Germany) combined with different levels of Lactose (Granulac 200, Meggle, Germany) were tested. As a low soluble model drug, riboflavin was added in a concentration of 1 % to the powder mixtures. Demineralized water was used as granulation liquid.

Levels of pectin/lactose ratio investigated was: 99/1, 80/20, 50/50 and 20/80.

• Preparation of pellets

Pellets were prepared using a twin-screw extruder (Micro 27 GL-28D, Leistritz, Germany). The extruder had 23 dies of 1 mm diameter and 2.5 mm length. The extruded mass was rounded in a spheronizer (RM 300, Schlüter, Germany) with cross-hatched plate of 300 mm diameter at 800 rpm for 5 minutes. The pellets were dried in a fluid-bed dryer at 50° C for 30 minutes (ST 2 EX, Aeromatic, Switzerland).

For each formulation the powder feed rate and the pump rate were varied in order to find the optimal moisture level for production of spherical pellets. The extrudate water content. were tested in steps of approximately 2 %.

The water content of the extrudate was determined gravimetrically after drying at 105° C for 24 hours.

• Characterisation of pellets

Each pellet batch was sieved and the fraction between 0.7 mm and 1.7 mm collected for further characterisation.

Size and shape of the pellets were characterized using an image analysis system (Leica Q500MC, Qwin, UK). Prior to processing of the images, care was taken to assure that all pellets were detected as single entities. 1 pixel correspond to 54 µm. 6 feret diameters were measured around each individual particle for 400 ± 50 particles; median, D25 and D75 were calculated. The length was defined as the longest feret diameter, while the breadth as the shortest. Aspect ratio was calculated as length divided by breadth.

Mechanical stability of the pellets was evaluated by a standard friability test (Ph.Eur., with included glass-beads for testing of pellets).

A disintegration test (Ph. Eur.) modified as described in [1] was performed both in 0.1 M HCl and phosphate buffer pH 6.8 at 37 °C. Two replicates.

The in vitro dissolution was tested according to the paddle method (Ph. Eur). 500 mg pellets were exposed to two different test media: 1 liter 0.1 M HCl and 1 liter phosphate buffer pH 6.8, at 37° C for 120 minutes at 50 rpm (n = 3-6). Release of riboflavin was measured spectrophotometrically (λ = 445, Shimadzu Photometer, Japan).

Results and discussion

Pectinic acid was found to be very well suited for preparation of pellets by extrusion/ spheronisation. Its capacity as an extrusion aid must be high since even formulations containing only 20 % of the polymer resulted in pellets (see table 1).

Table 1: Characteristics of pectinic acid pellets

Formulation pectin/lactose	water content %	% in fraction			Length [mm] median (D25-D75)	Aspect ratio median (D25-D75)
		0.7 – 1.0 mm	1.0 – 1.7 mm	> 1.7 mm		
99/1	55.8	25.8	72.8	1.1	1.63 (1.52–1.68)	1.21 (1.15–1.27)
80/20	46.2	27.6	70.2	1.8	1.68 (1.48–1.79)	1.26 (1.19–1.33)
50/50	38.8	13.0	86.3	0.5	1.68 (1.41–1.79)	1.26 (1.17–1.33)
20/80	25.7	2.5	91.4	5.2	1.79 (1.63–1.90)	1.25 (1.18–1.32)

As can be seen from table 1, formulations containing high amounts of pectin need a higher water level to produce pellets than formulations that mainly consist of lactose. It is a known fact that substances with a low solubility require a higher moisture level than more soluble substances [2].

Reducing the amount of pectin in a formulation results in a slightly increased length and breadth of the pellets, but the aspect ratio remains nearly constant. The extruded mass therefore seems to be more deformable, and some “shaping” is taking place during the spheronisation. This can be recognised as an increase in the fractions of larger particle sizes (1.0–1.7 mm and > 1.7 mm).

The shape and size of the pellets were not optimal (aspect ratio >1.1), however, a further optimisation of the moisture level should result in more spherical particles. No problems that could interfere with the plasticity/rigidity ratio (e.g. swelling of the polymer) were recognised. By employing a pectin derivative with a low solubility in water it was possible to overcome previous difficulties with other pectin qualities.

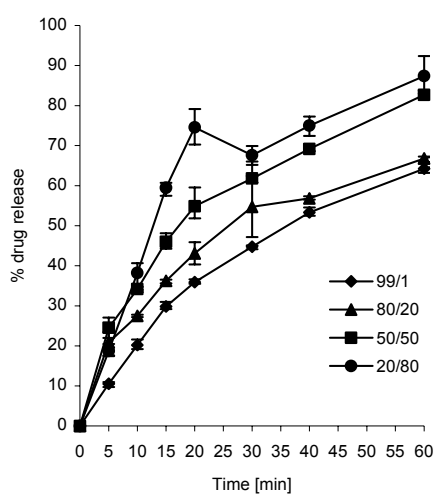


Fig. 1: Drug release in 0.1 M HCl (n= 3-6, error bars indicate min and max values)

Typical for the pectinic acid pellets was a partially disintegration within the 15 min. of the test. This is reflected in the results from the dissolution test (Fig.1). After 15 minutes in 0.1 M HCl, between 30 and 60 % of the low soluble model drug had been released. The release profiles in phosphate buffer pH 6.8 are similar to those in figure 1, but shifted slightly toward lower release values. These findings indicate an advantage for the pectinic acid pellets over MCC pellets, which are known to produce sustained release profiles.

Conclusion

The current investigation showed that pectinic acid has a great capacity as an extrusion aiding excipient for pelletisation by extrusion/spheronisation, although further work is needed in order to optimise the sphericity and reduce the size distribution.

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