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Note

Pectinic acid, a novel excipient for production of pellets by extrusion/spheronisation: preliminary studies

Ingunn Tho[a,*], Sverre Arne Sande[a], Peter Kleinebudde[b]

[a]*Department of Pharmaceutics, School of Pharmacy, University of Oslo, Oslo, Norway*
[b]*Institute of Pharmaceutics and Biopharmaceutics, Martin-Luther University, Halle-Wittenberg, Germany*

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Abstract

A very low soluble pectin-derivative (pectinic acid, degree of methoxylation 4%) was found to be well suited as an excipient for pelletisation by extrusion/spheronisation. Formulations containing pectinic acid and lactose in the following ratios were evaluated: 99/1, 80/20, 50/50 and 20/80. The capacity as an extrusion aid was found to be high; even formulations containing only 20% pectinic acid resulted in nearly spherical pellets. All pectinic acid pellets were mechanically stable, had an aspect ratio of approximately 1.15–1.20 and released 30–60% of a low solubility model drug within 15 min both in simulated gastric acid (0.1 M HCl) and intestinal fluid (phosphate buffer pH 6.8).

Keywords: Pectinic acid; Pellets; Extrusion/spheronisation; Image analysis; Dissolution profiles

1. 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 [1]. A disadvantage of MCC is that pellets based on MCC usually do not disintegrate, and as a consequence, especially low soluble drug substances are usually released slowly. Other excipients have been studied as an alternative to MCC in the last years [2–6].

Pectin, a naturally occurring polysaccharide, has been one of the candidates to be used as an excipient. Different types of pectin (degrees of methoxylation (DM) 35–72, and amid substitution) have previously been evaluated, but none of the types were capable of producing spherical products with a purely aqueous granulation liquid [7,8]. The reason was that polymer swelling caused lack of an appropriate plasticity–rigidity ratio for the extrudate, allowing it to break into pieces that resulted in spherical pellets.

The working hypothesis was that a less soluble derivative would be more suitable for production of spheres than the soluble, swelling qualities. The distinction between pectin and pectinic acid is per definition a DM of 10%.

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

2. Materials and methods

2.1. Materials

Formulations containing pectinic acid with a DM of 4% (Classic AU-L 049/01, Lot no. 0106214, Herbstreith and Fox GmbH, Germany) combined with different levels of lactose (Granulac 200, Meggle, Germany) were tested. As a low soluble model drug, riboflavin (Sigma–Aldrich Chemie GmbH, Germany) was added at a concentration of 1% to the powder mixtures. Demineralised water was used as granulation liquid.

Levels of pectinic acid/lactose ratio investigated were: 99/1, 80/20, 50/50 and 20/80.

2.2. 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 min. The pellets were dried in a fluid-bed drier at 50°C for 30 minutes (ST 2 EX, Aeromatic, Switzerland).

* Corresponding author. School of Pharmacy, University of Oslo, P.O. Box 1068, Blindern, N-0316 Oslo, Norway. Tel.: +47-22-85-65-98; fax: +47-22-85-44-02.

E-mail address: ingunn.tho@farmasi.uio.no (I. Tho).

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Table 1
Characteristics of pectinic acid pellets[a]

Formulation			Sieving analysis % in fraction			Image analysis median (D25–D75)			
Pectin/lactose ratio	Power consumption (%)	Water content (%)	0.7–1.0 mm	1.0–1.7 mm	> 1.7 mm	Length (mm)	Breadth (mm)	Aspect ratio	Area (mm^2)
99/1	10.4	54.3	31.3	68.2	0.3	1.81 (1.64–1.90)	1.21 (1.08–1.28)	1.25 (1.21–1.53)	1.59 (1.41–1.83)
99/1	**9.7**	**55.8**	**25.8**	**72.8**	**1.1**	**1.60** (1.48–1.67)	**1.27** (1.21–1.37)	**1.11** (1.07–1.17)	**1.55** (1.43–1.73)
99/1	9.0	57.4	13.6	72.9	13.5	1.65 (1.55–1.70)	1.44 (1.28–1.48)	1.10 (1.08–1.12)	1.81 (1.57–1.97)
80/20	12.0	42.2	18.8	81.2	0.2	1.91 (1.72–1.97)	1.31 (1.17–1.37)	1.40 (1.30–1.52)	1.79 (1.59–1.94)
80/20	11.3	48.0	12.7	68.6	0.8	1.78 (1.73–1.84)	1.33 (1.28–1.44)	1.23 (1.11–1.30)	1.74 (1.68–1.96)
80/20	**10.7**	**46.2**	**27.6**	**70.2**	**1.8**	**1.59** (1.48–1.74)	**1.24** (1.17–1.32)	**1.21** (1.09–1.24)	**1.47** (1.37–1.83)
50/50	12.3	28.1	4.9	94.1	0.5	1.95 (1.67–2.10)	1.33 (1.31–1.46)	1.32 (1.21–1.48)	2.10 (1.76–2.23)
50/50	**11.9**	**38.8**	**13.0**	**86.3**	**0.5**	**1.66** (1.56–1.72)	**1.34** (1.19–1.25)	**1.19** (1.11–1.31)	**1.61** (1.45–1.86)
50/50	10.7	39.6	7.0	74.9	18.0	1.68 (1.60–1.79)	1.44 (1.37–1.52)	1.13 (1.08–1.16)	1.84 (1.69–2.07)
20/80	13.9	25.1	1.5	97.2	0.7	1.94 (1.85–2.02)	1.38 (1.33–1.42)	1.36 (1.25–1.42)	2.03 (1.89–2.17)
20/80	**13.2**	**25.7**	**2.5**	**91.4**	**5.2**	**1.81** (1.64–1.90)	**1.45** (1.31–1.55)	**1.16** (1.12–1.22)	**1.92** (1.71–2.16)
20/80	11.7	26.9	2.5	67.5	29.4	1.90 (1.86–1.97)	1.64 (1.53–1.70)	1.13 (1.09–1.15)	2.40 (2.22–2.62)

[a] The most optimal shaped pellet batch of each formulation are given in bold.

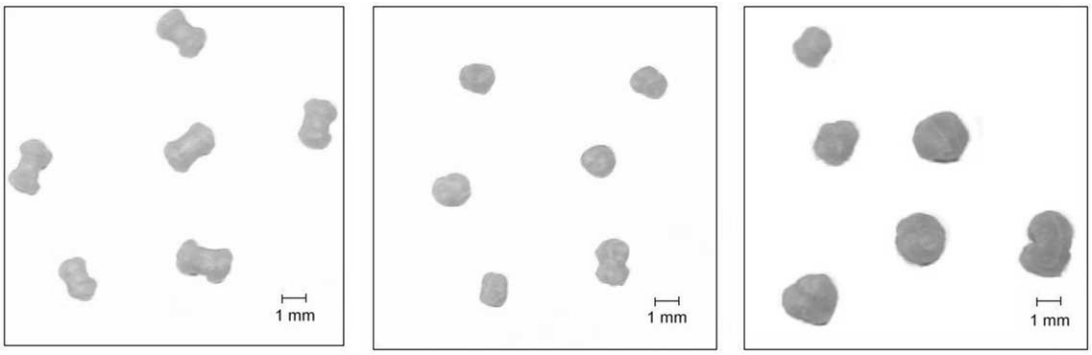

Fig. 1. Image of pellets of different levels of water content for pectinic acid/lactose ratio 99/1: (A) too low; (B) close to optimal; (C) too high.

For each formulation, different combinations of powder feed rate and pump rate were chosen in order to find a suitable moisture level for production of nearly spherical pellets. The extrudate water content was varied in steps of approximately 2%.

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

2.3. Size and shape of the pellets

Each pellet batch was sieved and the fraction between 0.71 and 1.7 mm collected for further characterisation. The pellets were characterised 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. One pixel corresponds to 22 μm. Six 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, the breadth as the shortest and the area calculated from the total number of detected pixel in one object. Aspect ratio was calculated as length divided by the feret orthogonal (at right angle) to the longest feret.

2.4. Mechanical stability

The pellets were evaluated by a standard friability test (Ph.Eur.) with included glass-beads for testing of pellets as described by Millilli and Schwartz [9].

2.5. Dissolution rate

The in vitro dissolution was tested according to the paddle method (Ph. Eur). Pellets (500 mg) were exposed to two different test media: 1 l of 0.1 M HCl and 1 l phosphate buffer pH 6.8, at 37°C for 120 min at 50 rpm ($n = 3$–6). The release of riboflavin was measured spectrophotometrically ($\lambda = 445$ nm, Shimadzu Photometer, Japan).

3. Results and discussion

Pectinic acid was found to be suitable for preparation of pellets by extrusion/spheronisation. The pectinic acid tested has a DM of 4%, a pH of 2.8 and is almost insoluble in water. Its capacity as an extrusion aid is high since even formulations containing only 20% of the polymer resulted in pellets (Table 1).

Table 1 reports the particle size and the size distribution (D25 and D75) for the different water levels tested per formulation in order to identify the adequate amount. When the water content was too low, the resulting products were rod-shaped to dumbbell-shaped particles (Fig. 1). Too high water levels resulted in high degree of deformation and tendencies towards snow-balling (Fig. 1). This is also recognised as an increasing breadth of the products as well as a larger area. The water level giving the most optimal shaped pellets within the tested limits was selected based on the lowest area.

None of the formulations was effective in producing

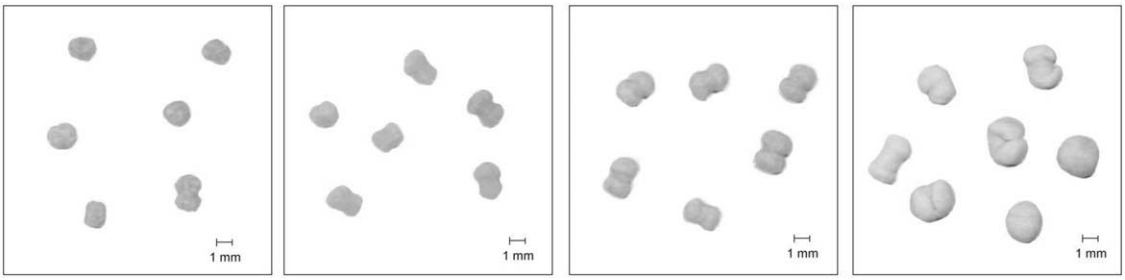

Fig. 2. Image of pellets of pectinic acid/lactose ratios: (A) 99/1; (B) 80/20; (C) 50/50; (D) 20/80.

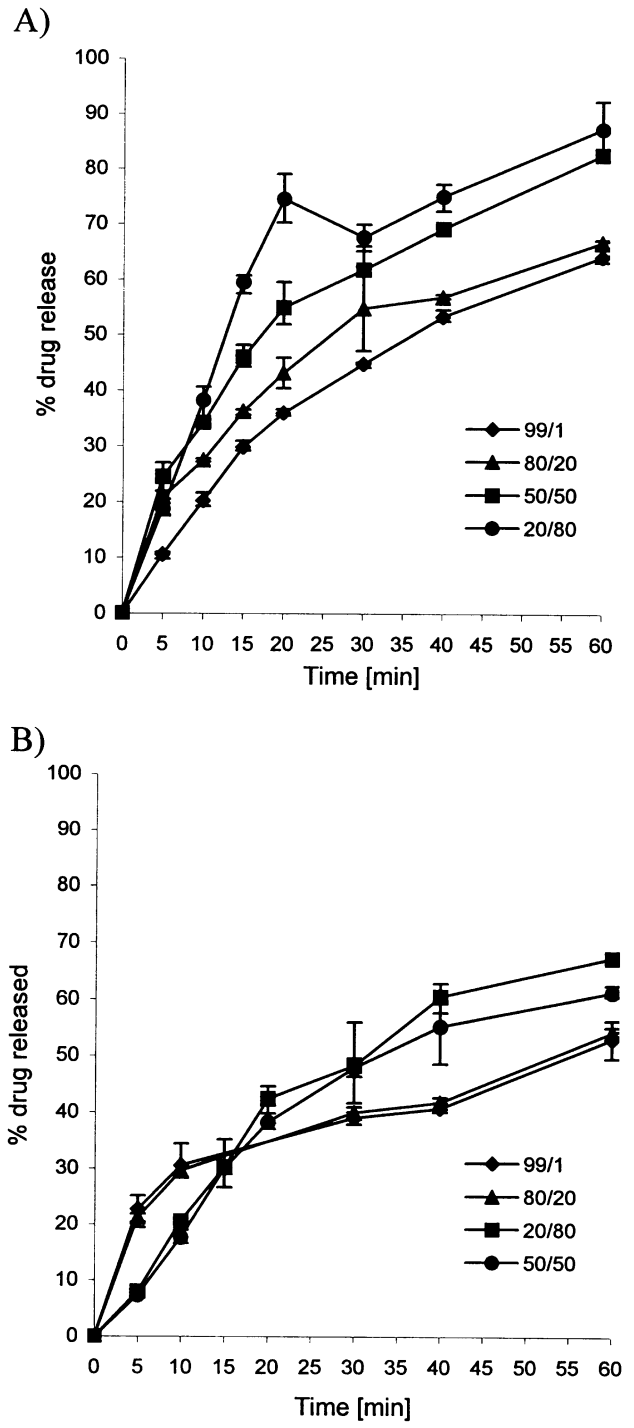

Fig. 3. (A) Drug release in 0.1 M HCl. (B) Drug release in phosphate buffer pH 6.8 ($n = 3$–6. Error bars indicate min and max values).

spherical pellets (aspect ratio >1.1), however, a further optimisation of the moisture level might probably result in more spherical particles. Problems concerning the plasticity/rigidity ratio (e.g. swelling of the polymer) were not revealed. By employing a pectin derivative with a low solubility in water, it was hence possible to overcome previous difficulties with other pectin qualities [7,8].

As can bee 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 generally recognised that substances with a low solubility require a higher moisture level than more soluble substances [10].

Reducing the amount of pectin in a formulation results in a slightly increased length and breadth of the pellets with a nearly constant aspect ratio. This is evident by an increase in the fractions of larger particle sizes (1.0–1.7 mm and >1.7 mm in Table 1 and Fig. 2). The different sizes of the pellets might be related to different extent of shrinking. A high fraction of pectinic acid requires a higher water content. During drying, a possible shrinking is therefore more pronounced, leading to smaller pellets.

After 15 min in 0.1 M HCl, between 30 and 60% of the low-soluble model drug had been released (Fig. 3). The release profiles in phosphate buffer pH 6.8 are similar to those in Fig. 3B, but shifted slightly towards lower release values. The pellets swell, break up and partly disintegrate. A pronounced change in morphology can be observed during dissolution. These findings may indicate a possible advantage for the pectinic acid pellets over MCC pellets, which are known to produce matrix type release profiles.

4. 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 to optimise the sphericity and to reduce the size distribution.

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