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Formulation of triamcinolone acetonide pellets suitable for coating and colon targeting

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Abstract

Spherical pellets containing 5% of triamcinolone acetonide (TA) were formed by extrusion/spheronization following formulation with microcrystalline cellulose (MCC) and/or a hydrophilic excipient (lactose, sodium carboxymethylcellulose or β-cyclodextrin, β-CD). Their suitability for coating, with a view to colonic drug delivery, was assessed in terms of their size, sphericity and dissolution test response. Best results were afforded by 5:90:5 MCC–β-CD–TA pellets obtained by complexation of TA with β-CD prior to addition of MCC, extrusion and spheronization. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: β-Cyclodextrin; Extrusion/spheronization; Pellets; Triamcinolone acetonide

1. Introduction

In the last decade there has been considerable progress in the development of dosage forms for colonic drug delivery (Mrsny, 1992; Van den Mooter and Kinget, 1995). One approach has been to enclose drug-loaded pellets in coatings that resist chemical and enzymatic attack in the stomach and small intestine but are degraded by colonic bacterial enzymes (Van den Mooter et al., 1994; Brondsted et al., 1995). Pellets are readily coatable (Sousa et al., 1995), are easily manufactured at high rates with a narrow size distribution favouring uniform drug-release behaviour (Woodruff and Nuessle, 1972) and have a short gastrointestinal transit time (Bechgaard and Ladefoged, 1978).

Among the drugs whose release in the colon is desirable is the glucocorticoid triamcinolone acetonide (TA). TA is more potent than sulfasalazine, the current drug of choice for

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Table 1
Circularities and Feret diameters of spheronized triamcinolone acetonide pellets with various excipient formulations, and the proportion of drug released after 2 h in a standard dissolution test

Formulation	MCC (%)	Water-soluble excipient		Wetting agent (ml)	Circularity	Feret diameter (μm)	% release after 2 h
		Compound	%				
1	95	–	–	42	0.92 ± 0.032	769.9 ± 72.52	8.37 ± 0.65
2	75	Lactose	20	30	0.94 ± 0.034	842.8 ± 102.59	5.77 ± 0.638
3	–	Lactose	95	10	–	–	–
4	90	NaCMC	5	57[a]	0.95 ± 0.033	793.73 ± 106.3	9.6 ± 1.12
5	85	NaCMC	10	48.2[a]	0.93 ± 0.043	960.3 ± 141.59	91.43 ± 1.14
6	85	β-CD	10	48	0.91 ± 0.035	1242 ± 9735	7.52 ± 0.561
7	45	β-CD	50	30	0.91 ± 0.037	949 ± 71.51	35.25 ± 2.04
8	15	β-CD	80	20	0.93 ± 0.04	638.3 ± 184.45	48.6 ± 0.521
9	5	β-CD	90	30	–	–	–

[a] Ethanol–water 1:1.

treatment of ulcerative colitis and Crohn's disease, but systemic uptake of TA following precolonic release and from conventional oral dosage forms gives rise to side-effects that can become serious during prolonged treatment. In this work we investigated the formulation of TA pellets suitable for coating and colon targeting.

Pellets investigated in this work all contained 5% of TA, 0–95% of microcrystalline cellulose (MCC) and 0–95% of a hydrophilic excipient [lactose, sodium carboxymethycellulose (NaCMC) or β-cyclodextrin (β-CD)]. MCC was initially chosen as the major excipient because of its past record of producing pastes suitable for extrusion and spheronization (Newton et al., 1992) and MCC/β-CD mixtures have also been found suitable for this purpose (Gazzaniga et al., 1995). Our objective was to identify a formulation affording granules that were sufficiently spherical for facile coating and released 80% or more of their TA load in the first 2 h of a standard dissolution test.

2. Materials and methods

2.1. Materials

Triamcinolone acetonide was purchased from Roig-Farma (Spain), microcrystalline cellulose (Avicel® PH 101) from FMC International (UK), sodium carboxymethycellulose from Sigma (Spain) and α-lactose monohydrate from De Melkindustrie Veghel (The Netherlands). β-Cyclodextrin was a generous gift from Roquette (Spain). The wetting agent for extrusion pastes was distilled water, except when NaCMC was

Table 2
Circularities and Feret diameters of spheronized triamcinolone acetonide pellets formulated by complexation of TA with β-cyclodextrin prior to addition of microcrystalline cellulose, extrusion and spheronization, and the proportion of drug released after 2 h in a standard dissolution test

Formulation	MCC (%)	β-CD (%)	Wetting agent (ml)	Circularity	Feret diameter (μm)	% release after 2 h
10	15	80	42.5	0.91 ± 0.037	1041.6 ± 51.75	53.4 ± 1.08
11	10	85	25+5	0.92 ± 0.036	1129.1 ± 63,13	65.65 ± 0.72
12	5	90	25	0.94 ± 0.035	1091.7 ± 165.2	98.83 ± 2.10
13	2	93	25	0.90 ± 0.044	480.2 ± 168.65	101.47 ± 1.17
14	–	95	28.5	0.92 ± 0.036	850.4 ± 183.89	99.87 ± 1.94

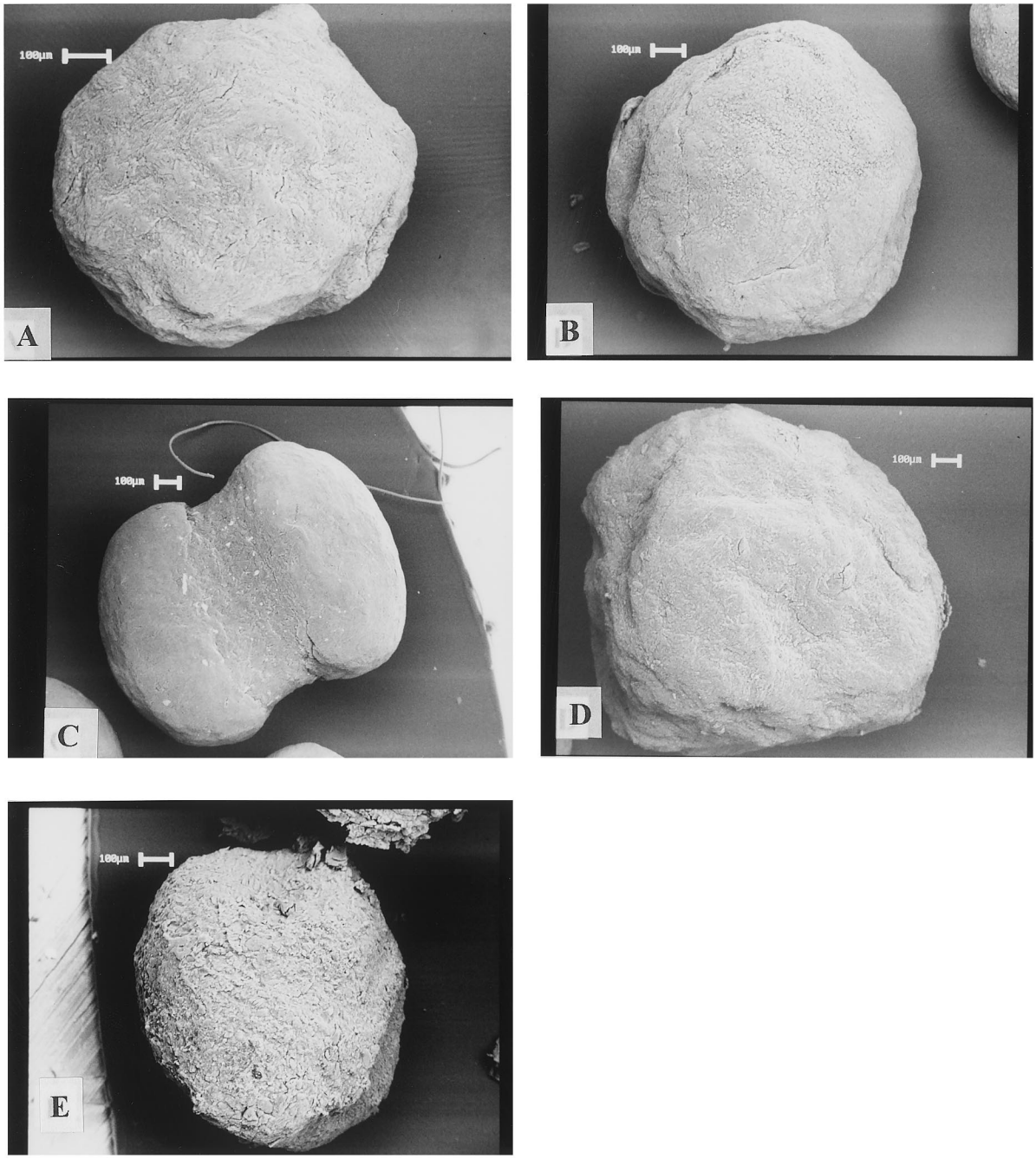

Fig. 1. Scanning electron micrographs of triamcinolone acetonide pellets with various excipients. (A) Avicel® (95%) and mixtures with (B) lactose (20%), (C) sodium carboxymethylcellulose (10%), (D) β-cyclodextrin (10%), (E) β-cyclodextrin (80%).

included, in which case a 1:1 mixture of distilled water and ethanol was used because water alone failed to produce an extrudable paste.

2.2. Methods

2.2.1. Pellet preparation

In a first series of experiments, pellets were formed by extrusion and spheronization as described below (Section 2.2.1.1). In a second series, undertaken for the reasons discussed below in Section 3, TA–β-CD complex was prepared by kneading prior to additon of MCC, and followed by extrusion and spheronization (see Section 2.2.1.2).

2.2.1.1. First series. The dry excipients and drug were mixed to homogeneity (15 min) in a Turbula T2C mixer. Distilled water was added in proportions listed in Table 1, and a paste of suitable consistency for extrusion was formed in an orbital mixer operated at 300–800 rpm. The paste was extruded through a 1.0-mm mesh screen in a Caleva Model 10 basket extruder (Caleva Ltd, UK) operated at 60 rpm, and the extrudates were spheronized for 25 min at 3000 rpm in a Caleva Model 120 spheronizer with a 12-cm friction plate. The spheronized pellets were dried for 24 h at 60°C in an oven (Heraeus, Spain) before storage at a relative humidity of 30%.

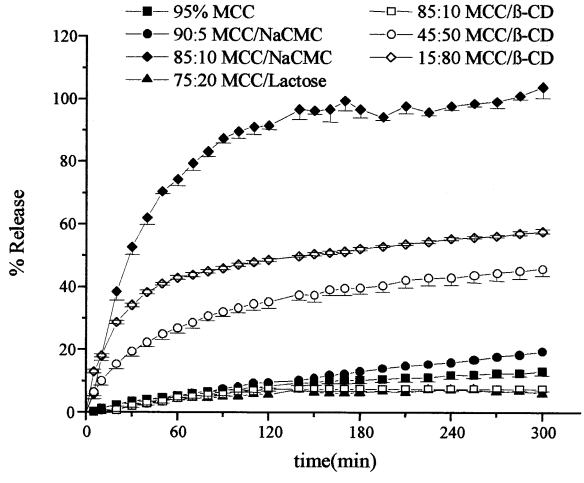

Fig. 2. Drug release from spheronized triamcinolone acetonide pellets with various excipients.

2.2.1.2. Second series. TA and β-CD were thoroughly mixed in an orbital mixer, water was added (see Table 2 for quantities), and mixing was continued at 500 rpm. MCC was added after about 3 h (except for Formulation 14), and after kneading to homogeneity the resulting paste was extruded, spheronized, dried and stored as described above for the first series of formulations.

2.2.2. Image analysis

For each formulation, the Feret diameters and circularities of 600 particles were determined microscopically by digital image analysis using the program PC Image VGA 24 v.2.1 (Foster Findlay Associates, UK) running of a computer connected to a video camera on an Olympus SZ60 stereomicroscope.

2.2.3. Dissolution studies

Drug release was evaluated in dissolution studies using the Paddle Method no. 2 (USP XXIII edition). A quantity of pellets containing 10 mg of TA was stirred for 5 h at 100 rpm in a Prolabo Dissolutest apparatus containing 1 l of 0.2 M phosphate buffer at 37 ± 0.5°C. The TA content of samples taken periodically was determined by measuring absorbance at 242 nm in a Hewlett-Packard 8452A spectrophotometer.

2.2.4. Solubility studies

The solubility of TA in water in the presence of various concentrations of β-CD was determined by the method of Higuchi and Connors (1965). Excess TA (40 mg) was added to tubes containing 10 ml of 0-17.62 mM solutions of β-CD in distilled water, and the tubes were shaken for 7 days at 80 cycles/min in a water bath thermostatted at 37 ± 0.5°C, after which the concentration of TA in samples passed through 0.45-μm cellulose nitrate filters was determined spectophotometrically at 242 nm. The apparent 1:1 stability constant (K) was calculated from the linear part of the phase solubility diagram.

2.2.5. Scanning electron microscopy

Both dissolution-tested (after 5 h in 0.2 M phosphate buffer) and non-dissolution-tested pellets were examined by scanning electron mi-

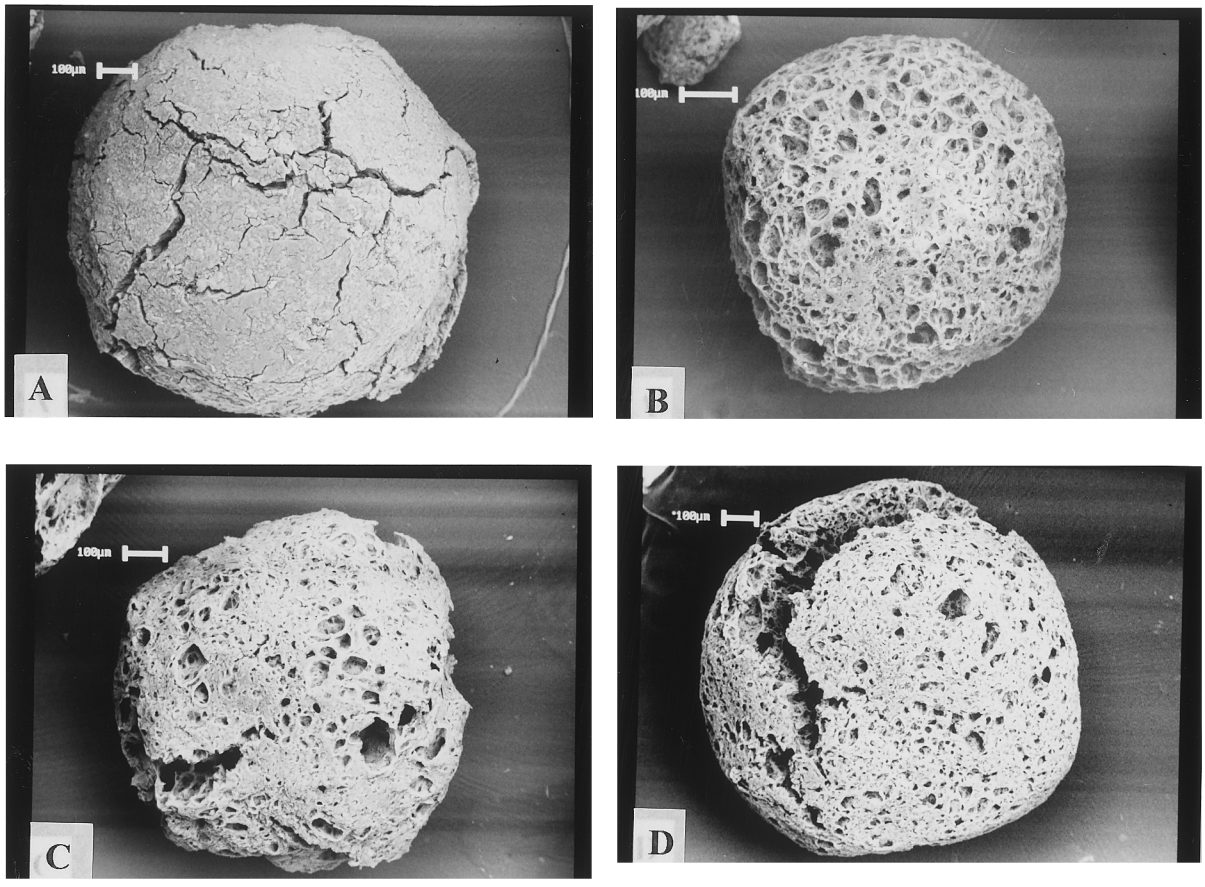

Fig. 3. Scanning electronmicrographs of triamcinolone acetonide pellets after a 5-h dissolution test. Without kneading: (A) Avicel® (95%), (B) β-cyclodextrin (80%). With kneading: (C) β-cyclodextrin (80%), (D) β-cyclodextrin (90%).

croscopy (Leo 435 VP, UK). Samples were sputter-coated with gold and mounted on double-stick tape on a carbon grid.

3. Results and discussion

Table 1 lists the first series of formulations assayed. The formulations with lactose alone as excipient or with 90% β-CD failed to allow formation of extrudable pastes. For the other formulations, Table 1 also lists the circularity and Feret diameter of the pellets formed, and the percentage of TA released during the first 2 h of the dissolution test. The mean circularities, 0.91 or better in all cases in which pellets were obtained, indicate a sphericity that is sufficient for facile coating (Fig. 1). The mean diameters, which range from 638 to 1242 μm, can be assumed to be subject to modification by variation of the quantity of wetting agent used for pelletization.

Fig. 2 shows the drug-release profiles recorded in the dissolution test. This test was survived by all pellets except those formulated with 10% of NaCMC, which swelled and disintegrated. The formulation with MCC alone as excipient was the first to be assayed. In view of its poor drug-release response (Fig. 2), formulations containing a hydrophilic excipient were tested. The first hydrophilic excipient tried was lactose, on account of its high solubility in water. As noted above, the lactose-only formulation was unextrudable (in

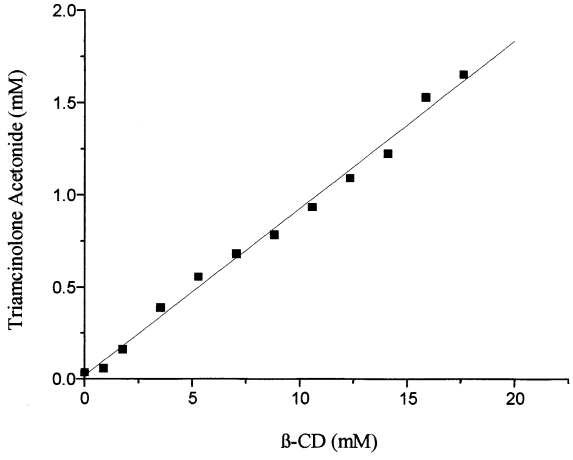

Fig. 4. Solubility of TA in aqueous solutions of β-CD at 30°C.

spite of the minimal proportion of water used), and a 75:20 MCC–lactose formulation had an even poorer drug-release response than the MCC-only formulation. A 90:5 MCC–NaCMC formulation failed to improve drug release significantly, and the 85:10 MCC–NaCMC formulation was ruled out, in spite of its excellent dissolution profile (Fig. 2), because it swelled and disintegrated during the test (swelling as the result of the permeation of fluid through a film coating in precolonic regions of the gastrointestinal tract would doubtless cause rupture of the coating and premature drug release (Papadimitriou et al. 1993)).

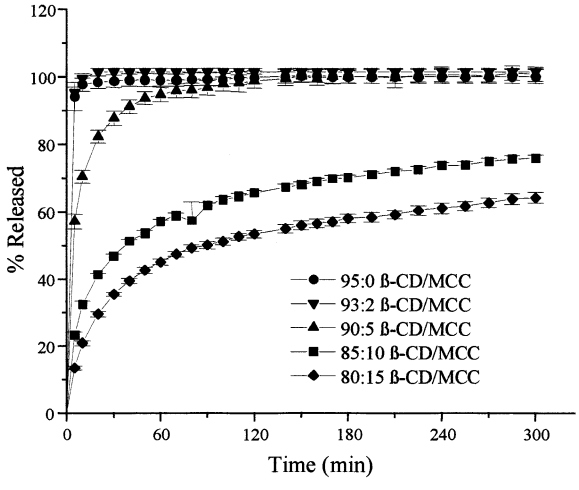

Fig. 5. Drug release from triamcinolone acetonide pellets prepared by complexation of TA with β-cyclodextrin prior to addition of microcrystalline cellulose, extrusion and spheronization.

Including just 10% of β-CD in the formulation likewise failed to improve drug release, but in this case the cause seemed likely to be that better intrinsic drug release characteristics were being offset by the significant increase in granule size associated with the large amount of water required for preparation of an extrudable paste. When higher proportions of β-CD were employed, less water was needed, granule size fell and drug release improved, reaching almost 50% within 2 h in the 15:80 MCC–β-CD formulation. However, attempts to improve drug release further by further increasing β-CD content failed because of unextrudability (as noted above).

With a view to finding out whether the beneficial effect of β-CD on drug release might be augmented in some way, we investigated whether this effect might be due not only to the enhancement of particle porosity upon dissolution of β-CD (Fig. 3), but also to the dissolving β-CD carrying with it TA bound in its cavity. The formation of a soluble TA–β-CD complex (with a calculated stability constant of 2800 M^{-1}) was confirmed by solubility experiments affording an A_L type diagram (Higuchi and Connors, 1965), the solubility of TA increased linearly with β-CD concentration (Fig. 4).

This finding suggested that the promotion of TA–β-CD complex formation by kneading a TA–β-CD mixture prior to addition of MCC might favour the subsequent release of TA into the dissolution test medium. Accordingly, the second series of experiments described in Section 2.2.1 was undertaken (Table 2).

The procedure used for the second series of formulations allowed the formation of extrudable pastes with higher β-CD contents than in the first series; pellets with 95% β-CD and no MCC now had sizes and circularities similar to those formulated with MCC alone (Tables 1 and 2). The complex promotion procedure increased the proportion of TA released by the 15:80 MCC–β-CD

formulation from 49 to 53% in spite of a parallel increase in granule diameter from 638 to 1042 μm. Increasing β-CD content reduced granule size and further increased drug release (Fig. 5): nearly 100% release was achieved with formulations containing $\geq 90\%$ of β-CD, but pellets with MCC contents less than about 5% disintegrated in the dissolution medium. It is therefore Formulation no. 12 (5:90:5 MCC–β-CD–TA) that will be used in studies aimed at optimizing pellet coating for colonic drug delivery.

4. Conclusions

TA pellets formed by extrusion/spheronization present proper size and circularity when hydrophilic excipients are used. MCC–β-CD–TA 5:90:5 pellets obtained by complexation of TA with β-CD prior to addition of MCC, extrusion and spheronization have high sphericity (which should facilitate application of a coating resistant to the gastric and small intestinal media), retain their integrity in dissolution medium (which suggests that coatings will not burst prematurely due to granule swelling) and release their TA load rapidly in a standard dissolution test.

Acknowledgements

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