Journal of Drug Delivery Science and Technology xxx (2017) 1–11

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Cellulose-polysaccharide film-coating of cyclodextrin based pellets for controlled drug release

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ARTICLE INFO

Article history:
Received 27 February 2017
Received in revised form
30 March 2017
Accepted 30 March 2017
Available online xxx

Keywords:
Triamcinolone acetonide
β-cyclodextrin pellets
Ethylcellulose-pectin membranes
Extrusion-spheronization
Fluid bed coating

ABSTRACT

An oral controlled release system based on blends of ethylcellulose and pectin as film-coating material for pellets was developed. Triamcinolone acetonide (TA) as drug useful in intestinal inflammatory disorders was loaded into cyclodextrin-based pellets. The combination of pectin and ethylcellulose as coating materials was investigated in terms of mechanical analysis, viscosimetry, DSC and TGA, water vapor permeability and TA diffusivity using membranes prepared at different ratios. The coating process by fluid bed coating system was used to obtain different thicknesses of coating for pellets previously fabricated by extrusion-spheronization. To investigate the influence of coating on controlled release properties, the microstructure, specific surface area, porosity and TA release profile from pellets were also assayed.

The versatility of the system has been proven by selecting different combinations of blends of polymers. Further, by the reduction in the proportion of pectin in the ethylcellulose:pectin membrane and increasing the thickness of coating, it was possible to achieve a prolonged release over pH 6. These results suggest that the delivery system based on pectin:ethylcellulose coating for pellets has an excellent colon release performance for TA providing protection for drugs that are unstable at acidic pH.

1. Introduction

Multiparticulate drug delivery systems (MDDS) are attracting interest in the last decades for administering drugs by oral route, due its functionality to obtain an effective controlled drug release according to the biomedical application. Multiparticulate dosage forms as pellets can offer numerous biopharmaceutical advantages over other conventional solid forms such as reducing the GI adverse effects (less local irritation), longer transit times, high loading of drug, uniform drug content and drug-release behavior, and the flexibility to be administered in other pharmaceutical dose forms, in capsules or tablets [1,2].

MDDS are especially suitable to achieve a sustain release of the drug and the delivery of the active substance to the specific absorption site in the gastrointestinal tract. However, pellets obtained by extrusion-spheronization techniques normally exhibit very slow release properties, particularly when the drug shows low aqueous solubility. One of the main reasons for this behavior is because microcrystalline cellulose, usually the most widely excipient used as pelletization aid [3,4], result in hampering the release of low soluble drugs [4,5]. Regardless of the good properties of microcrystalline cellulose to obtain spherical particles or smooth surface properties by this technique, the reluctance offered by pellets fabricated with this excipient to disintegrate even though disintegrating agents have been included in the formulation, hinders exploitation of the advantages of pellets when fast or programmed release is desired [5]. To avoid these problem different excipients has been proposed [5–10].

This work is based on a previous research where an alternative approach based on the use of the oligosaccharide β-cyclodextrin as main excipient in the process of extrusion-spheronization. Villar et a l in 1999 [6] formulated β-cyclodextrin-based pellets with fast-releasing behavior of the poorly soluble drug triamcinolone acetonide, with the aim to retain the drug for prolonged times until the formulation reaches the colon, the target site. β-cyclodextrin pellets were observed to have a suitable size and a shape for being coated by fluid bed technologies.

Natural Pectin polysaccharides has been described as a good

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http://dx.doi.org/10.1016/j.jddst.2017.03.031
1773-2247/

materials to obtain edible coatings in food [11]. It has been also used as component in the formulation of coated pectin-based matrix tablets [12] and pellets [13] for colon-specific drug release.

Ethylcellulose is a polymer that has been used in mixtures with another natural macromolecules as pectin [13], amylose [14], soy polysaccharides [15] or guar gum [16].

Triamcinolone acetonide (TA) has proven usefulness in the suppression of the clinical manifestation of inflammatory bowel disease (ulcerative colitis and Crohn's disease). As many other corticosteroids, TA has a very low solubility in water and its systemic absorption after the oral administration but previous to the desirable colonic delivery, involves a considerable number of adverse effects. The side effects are the limiting factor for the use of this valuable drug today. Considering these points, the development of a controlled drug delivery system is becoming increasingly important in the treatment of inflammatory bowel disease, not only to facilitate the drug efficacy against inflammation, but also to reduce the adverse effects associated that can become as serious complications in chronic treatments. In the present work, an attempt was made to prepare an oral film coating pellet delivery system of triamcinolone acetonide, a poorly soluble drug, with the ability to deliver the drug in different areas of the gastrointestinal tract including the colon. With this aim, ethylcellulose:pectin membranes as coating agent for β-cyclodextrin pellets have been explored as controlled release systems along with the influence of composition and thickness of coating on Triamcinolone acetonide (TA) release.

2. Materials and methods

2.1. Materials

Triamcinolone acetonide was supplied by Fagron Ibérica (Spain), Ethylcellulose (EC, Surelease®, Colorcon®), pectin from apple (AP) methoxylation degree 7.8% (Sigma, Spain), pectin from citrus fruit CP1 methoxylation degree >10% (Sigma, Spain), pectin from citrus fruit USP CP2 methoxylation degree >10% (Plimag Iberica), pectin from citrus fruit USP CP3 methoxylation degree >10% (Copenhagen Pectin A/S), Dibutylsebacate (DBS) (Sigma, Spain) and Pectinex Ultra SP-L activity 26000 PG/mL (Novo Nordisk, Spain). Microcrystalline cellulose (Avicel® PH 101) was purchased from FMC International (UK). β-Cyclodextrin was generously gifted by Roquette Frères (Vecquement, France).

2.2. Methods

2.2.1. Preparation of membranes by solvent cast technology

Initially, dispersions of 2% (w/w) of pectin in water were prepared and mixed with dibutylsebacate (DBS; used as plasticizer) and Surelease® at different ratios (see Table 1) by magnetic stirring during 2 h.

Membranes were prepared by solvent casting method. 600 mg of the dispersion (Table 1) were placed on PVDF cylindrical plates and dried at 60 °C from 12 h under vacuum. The fabricated membranes were carefully removed from the PVDF plates. After, membranes were analyzed for any fracture or deformations and their thickness were measured using a digital micrometer (Mitutoyo, Spain). The final mean thickness of the membranes was 150 μm.Finally, membranes were stored in plastic bags at ambient temperature.

2.2.2. Rotational viscosimetry

Pectin dispersions in water was characterized using a rotational viscosimeter Brookfield DV II Measurements were made in triplicate in 2% (w/w) pectin dispersions using shear rates of 0.39–39.53 s^{-1}.

Table 1
Composition of the membranes. EC: ethylcellulose, EW: equivalent weight, DBS: Dibutylsebacate.

Ratio EC/P	DBS %	Surelease (g)	EW EC (g)	DBS (g)	EW Pectin (g)
1:0	3	2.33	0.582	0.018	0
1:1	0	1.2	0.3	0	0.30
	3	1.16	0.291	0.009	0.30
3:1	0	1.8	0.45	0	0.15
	3	1.75	0.436	0.0135	0.15
4:1	0	1.92	0.48	0	0.12
	3	1.86	0.466	0.0144	0.12
5:1	0	2	0.5	0	0.10
	3	1.94	0.485	0.015	0.1
	6	1.88	0.47	0.030	0.1
	25	1.5	0.375	0.125	0.1
	35	1.3	0.325	0.175	0.1
7:1	3	2.04	0.509	0.016	0.075
20:1	3	2.2	0.55	0.017	0.029

2.2.3. Differential scanning calorimetry (DSC)

A differential scanning calorimeter (Shimadzu DSC-50) was used. 3–5 mg of samples were accurately weighted on sealed (DSC) aluminium pans and heated at a rate of 10°C/min from 25 °C to 300 °C (DSC).

2.2.4. Water vapor permeability determination

Round fragments of membranes of 1.1 cm of radius were punched out by means of a metal puncher of 2 cm of diameter. Glass vials were filled with 10 ml of water and membranes were placed in the exit hole of the vials and sealed with threaded screw plugs. The surface of the membrane were in contact with the external environment was 3.14 cm^2. A control sample was prepared also in a in the same conditions and without the membrane. Each experiment was performed intriplicate. The vials were stored in a desiccator containing silicagel at ambient temperature. Loss of weight was monitored at 24, 48 and 168 h.

The Moisture Vapor Transmission Rate (MVT; m^{-2} $(24h)^{-1}$) measurements were recorded was according to the ASTM recommendations using the following equation:

$$MVT = 24 \cdot g_{/A \cdot t}$$

where g is the weight variation, A is the surface (m^2) and t is the time. 24 is a correction factor to convert the time into a 24 h scale.

2.2.5. Mechanical analysis

The mechanical resistance of the membranes was determined by sextuplicate by tensile test experiment using a universal testing machine Lloyd LR5K (Lloyd Instruments, Ametek Co, Inc). Membranes were cut in fragments of 25 mm of length and 5 mm of width and tightened by two clamps maintaining a distance between clamps of 5 mm. The tension test speed was 5 mm/min and the force-displacement curve was recorded during the experiment to determine different parameters related to the mechanical resistance of the membranes: The young modulus, breaking strength and stress.

2.2.6. Triamcinolone acetonide diffusivity across membranes

Diffusion experiments were carried out using side-by-side diffusion cells (Crown Glass Co., Inc, USA) with a volume of both compartments of 3.4 ml. Membranes were placed between the compartments of the cell, allowing for an effective area of diffusion of 0.79 cm^2. The receptor medium was HCL 0.1 N or phosphate buffer (pH 6) and the donor medium was composed on a saturated solution o Triamcinolone acetonide in water. Compartments were kept under continuous stirring and at 37 °C during the experiment.

Please cite this article in press as: E.V. López, et al., Cellulose-polysaccharide film-coating of cyclodextrin based pellets for controlled drug release, Journal of Drug Delivery Science and Technology (2017), http://dx.doi.org/10.1016/j.jddst.2017.03.031