PECTIN-BASED COATINGS FOR ORAL COLON DRUG DELIVERY: APPLICATION BY POWDER-LAYERING TECHNIQUE

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INTRODUCTION

Oral colon delivery has widely been investigated for improved treatment of local disorders, mainly inflammatory bowel disease (IBD), and is also of interest for non-invasive administration of biologics. Furthermore, it is drawing attention as a strategy to replenish the microbiota and face dysbiosis conditions.

For colonic release, pectin, a D-galacturonic acid-rich hetero-polysaccharide found in plant cell walls, has extensively been used in view of its degradability by the resident bacteria (Liu L et al, Biomaterials 24, 3333, 2003). Pectin-based coatings have been obtained by double-compression or spray-coating. However, double-compression involves low flexibility in the core size and coating thickness as well as difficulties in centering the tablet core into the press die (Maroni A et al, J Drug Deliv Sci Technol 32, 229, 2016). With spray-coating, the main problem encountered is the high viscosity of the aqueous polysaccharide solutions. This requires the use of diluted coating formulations, leading to high energy consumption for solvent evaporation and long process times.

Recently, powder-layering, which is normally used for application of drugs onto inert cores, has been proposed for the application of time-dependent functional coatings based on low-viscosity hydroxypropyl methylcellulose, HPMC (Foppoli A et al, Drug Dev Ind Pharm 46, 1230, 2020). Using powder-layering, the processing time was considerably reduced compared to spray-coating, and the process yield was enhanced.

AIM

To evaluate the feasibility of powder-layering in the manufacturing of colon delivery systems provided with pectin coatings.

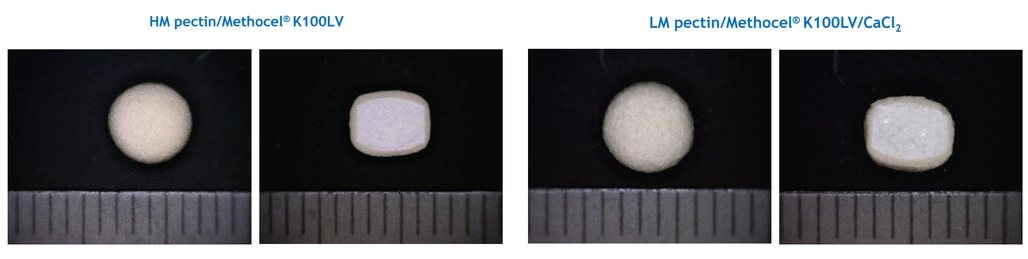

Fig. 1. photographs of systems coated with LM or HM pectin and Methocel™ K100LV, intact and cross-sectioned.

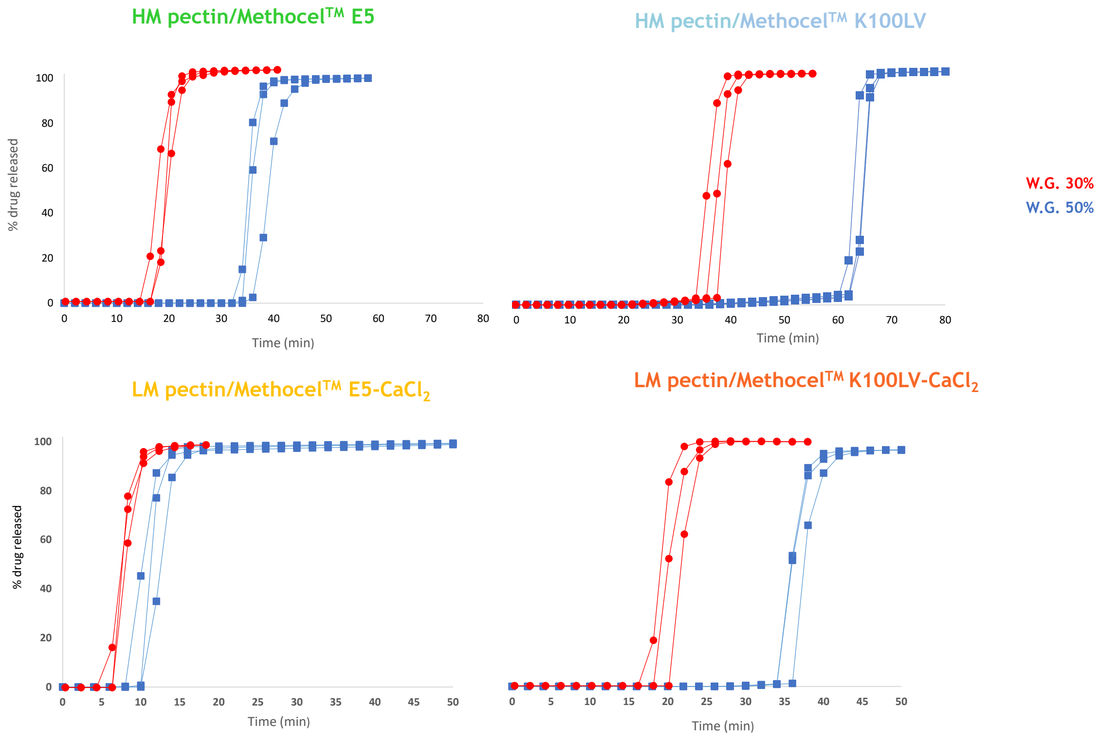

Fig. 2. Release of tracer drug from HM or LM pectin-coated tablets using Methocel™ E5 or Methocel™ K100LV as binding agent, in phosphate buffer pH 6.8.

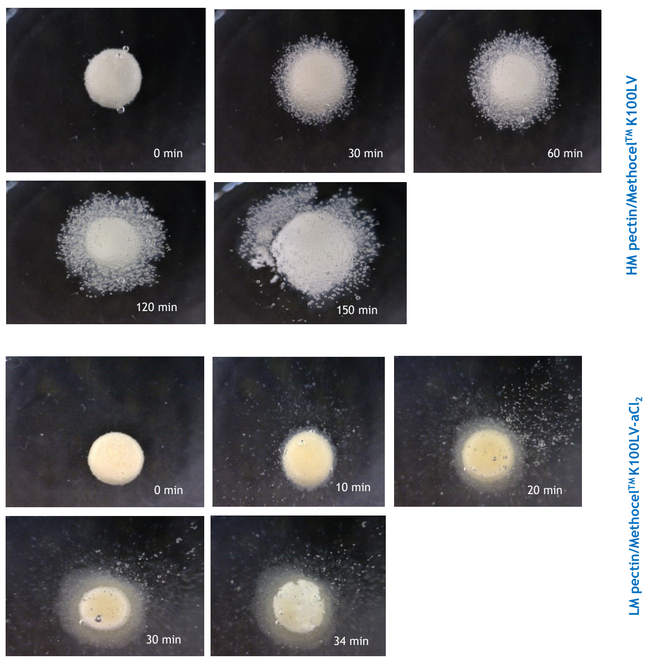

Fig. 3. Photographs of LM or HM pectin-coated systems immersed in deionized water at successive time points.

Fig. 4. Photographs of fluid bed equipped with a) rotor insert (tangential-spray) and b) three-way spray system.

Tab. I. Equipment and process parameters used for coating

	Powder-layering		
	Sealing	Coating	Drying
Equipment		Tangential-spray fluid bed	
Inlet air temperature (° C)	60	60	60
Outlet air temperature (° C)	32-35	30-32	32-36
Product temperature (° C)	32-36	30-32	32-36
Rotating disk speed (rpm)	400	400	400
Nebulization air pressure (bar)	2	2	2
Nozzle diameter (mm)	1.2	1.2	1.2
Air flow (m^3/h)	60	60	60
Spray rate (g/min/kg)	12-13	12-13	-
Powder loading speed (g/min)	-	2	-
Time (min)	30	variable	10

RESULTS AND DISCUSSION

Pectin with a high degree of methoxylation (HM), capable of forming a persistent gel, or low degree of methoxylation (LM), which instead requires bivalent cations, was used.

Under the operating conditions set up, the process weight gains with both pectin grades ran smoothly up to 30 and 50 % nominal, with only few technical interruptions (Tab. I,II). This was in contrast with spray-coating, which generally involves several stops to face nozzle clogging and powdering problems when dealing with aqueous solutions of polysaccharides having inherent stickiness characteristics.

Low-viscosity HPMC was found to be a superior binder as compared with pectin, either LM or HM.

Rather thick layers with a relatively rough surface were obtained, as expected based on the inherent porous structure (Tab. II; Fig. 1). However, powder-layering technique was shown flexible in the achievement of the desired coating level, which is a clear advantage over double-compression.

Such coatings were proved able to impart, as desired, a lag phase before release and prevent the outward diffusion of the drug prior to the release pulse (Fig. 2). LM pectin exhibited poor release control properties due to the tendency to rapidly dissolve in aqueous fluids and limited persistence of the gel barrier formed upon hydration (Tab. II; Fig. 2,3). On the other hand, HM pectin was shown more effective in delaying the onset of release.

HPMC also affected the duration of the delay phase: the selection of a proper viscosity grade and concentration in the binding solution, balancing the relevant sprayability and suitability for promoting powder deposition, was helpful in enhancing the performance of the coating.

Tab. II: coat thickness, weight gain and lag time of coated systems

Formulation code	thickness (µm)	w.g. (%)	$t_{10\%}$ (min)
HM pectin/Methocel™ E5	279.5	31.4	19.1±3.5
	438.5	53.5	37.9±4.0
HM pectin/Methocel™ K100LV	251.8	31.5	39.4±3.7
	385.1	50.6	65.5±4.2
LM pectin/Methocel™ E5-$CaCl_2$	259.4	29.3	6.5±0.9
	388.2	46.5	11.8±2.5
LM pectin/Methocel™ K100LV-$CaCl_2$	259.4	28.1	20.9±2.8
	390.9	46.7	37.4±2.8

MATERIALS AND METHODS

Immediate-release tablets were prepared from an 80% paracetamol (Rhodapap™ DC90, Novacyl, CN), 12.5% Avicel® PH101 (FMC, IT), 4.5% Explotab® CLV (JRS Pharma, IT), 2.0% Kollidon® VA64 (BASF Italia, IT), 0.5% Aerosil® 200 (Evonik Degussa Italia, IT) and 0.5% magnesium stearate (Carlo Erba Reagents, IT) powder blend (Turbula mixer, W.A. Bachofen, CH; 12+3min, 200rpm). Tableting was performed by a rotary press (AM-8S, Officine Ronchi, IT) equipped with concave punches (4mm diameter and curvature radius). The tablets (40 mg nominal weight) were coated by powder-layering in a tangential-spray fluid bed (GPCG1.1, Glatt, DE) equipped with a three-way nozzle with low-methoxyl (LM, Aglupectin LC-S12P, JRS Silvateam Ingredients, IT) or high-methoxyl (HM) pectin (Aglupectin HS-RP, JRS Silvateam Ingredients) after sealing with a 5% w/w Methocel™ E5 (HPMC, Colorcon, UK) or 3% w/w Methocel™ L100LV (Colorcon) solution that were used as the powder-layering binders (Figure 4). In the case of LM pectin, $CaCl_2$ (1%; Merck KGaA, DE) was added to the HPMC binding solutions. The process parameters set up are reported in Table I. The coated systems were characterized for weight gain (w.g.), thickness of the coatings (digital micrometer, Mitutoyo, IT; n=20) and morphological aspect (intact and cross-sectioned), and tested for release using an adapted USP43 disintegration apparatus (Sotax DT 3, Sotax, CH; 31 cycle/min, 800mL phosphate buffer-PB-pH 6.8, 37±0.5°C, UV assay at 248nm). The lag time was expressed as the time to 10% release ($t_{10\%}$). The coated systems were also statically immersed in deionized water at room temperature, and photographs were taken at successive times.

CONCLUSIONS

Powder-layering was demonstrated to be an adequate technique for applying pectin coatings that would defer the onset of drug release, as required for time-dependent colon delivery, and undergo microbial degradation once the coated systems reach the target site.

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