Original Research Article

Design of Sustained-Release 5-FU Pectinate Spheroids Using Ethyl Cellulose and Cyclodextrins

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ABSTRACT

Colon-specific drug delivery system is commonly designed through protection of core from upper gastrointestinal fluid via coating typically by means of a mixture of hydrophilic biodegradable polymer such as pectin and hydrophobic polymer such as ethyl cellulose (EC). However, the leaching of pectin from coat composite creates aqueous channels or water-filled pores and leads to fast drug release prior to dosage form reaching the colon region. This study formulates 5-FU into multi-particulate spheroids using pectin as both core and coating substances, combined with EC and cyclodextrins, to prevent early release and enhance drug delivery to the colon for colorectal cancer treatment. A partial replacement of pectin coat in pectin-EC mixture with β-cyclodextrin further reduced the propensity of drug release. However, using acetyl containing cyclodextrin series as coat additive, unexpectedly fast drug release was noted from zinc pectinate spheroids. Hydrophobic part of cyclodextrin exhibited preferential binding to EC. It gave rise to different coat domains from pectin and discontinuity in drug release barrier thereby prompting fast drug release.

Keywords: Colon-specific drug delivery, pectin, ethyl cellulose, 5-fluorouracil, cyclodextrin, extrusion-spheronization.

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Received: 04 Apr 2025; accepted: 24 Sept 2025
Available online:15 Nov 2025
http://doi.org/10.24191/IJPNaCS.v8i2.06

1.0 Introduction

Colon-specific drug delivery is crucial for treating local diseases like colorectal cancer (1-3). For decades, 5-FU, a pyrimidine analogue, has been the primary chemotherapy for this cancer, inhibiting RNA function and thymidylate synthesis (4,5). However, intravenous 5-FU causes severe systemic toxicity due to its effects on non-target tissues (6,7). The preferred administration route remains oral, requiring formulations that prevent premature drug release in the stomach and small intestine (8-10).

Colon-specific drug delivery systems are available as single-unit or multi-particulate forms, with the latter preferred for increased bioavailability, reduced toxicity, and consistent gastric emptying (11,12). Spheroids, a type of multi-particulate dosage, are gaining interest due to their small size and uniform drug absorption (13). Controlled release can be modulated via matrix coating, influenced by spheroid size, shape, and surface texture. Extrusion-spheronization is a key process in manufacturing these controlled-release systems (14).

Pectin, a natural polysaccharide resistant to upper gastrointestinal enzymes, is widely used in colon-specific drug delivery (15,16). Calcium ions are the most common crosslinking agent employed in processing of pectin matrix (17,18). The recent studies have replaced calcium ions with zinc ions, which are less selective but lead to the formation of stronger crosslinkages within a pectin matrix whose stability in the upper gastrointestinal tract is improved (19). The pectin is an aqueous soluble polymer and it undergoes partial degradation at gastric pH 2–4 via side chain hydrolysis and at small intestinal pH 5–6 via β-elimination of main chain or de-esterification (20). The matrix of pectin tends to swell, erode and has premature drug release at upper gastrointestinal tract (21,22). Combining pectin with hydrophobic polymers, like EC, improves its integrity, reducing early dissolution while allowing drug release in the colon's bacterial environment (2,23,24).

Cyclodextrins, cyclic oligosaccharides with *D*(+)-glucopyranose subunits linked by α-(1,4) glycosidic bonds, help target drug release to the colon (25-27). β-cyclodextrin, with low water solubility, is degraded by colonic bacteria, increasing coat porosity and enhancing drug release (28,29).

This study formulates 5-FU into multi-particulate spheroids using pectin as both core and coating substances, combined with EC and cyclodextrins, to prevent early release and enhance drug delivery to the colon for colorectal cancer treatment. Cyclodextrins are hypothesized to act as a molecular ‘bridge’ between hydrophilic pectin and hydrophobic EC, thereby facilitating better interaction between the two polymers.

2.0 Materials and Methods

2.1 Materials

Pectin (Classic CF 301, degree of esterification = 65-70%, Herbstreith & Fox, Germany) was employed as a matrix polymer for spheroids. EC (Ethocel 100 standard premium, Colorcon, Singapore) was used as a hydrophobic coating polymer for spheroids with triethyl citrate (TEC, Merck, Germany) as plasticizer. 5-fluorouracil (5-FU, AoBo Bio-Pharmaceutical Technology Co., Ltd. Shanghai) was used as the drug of choice for colon delivery. Microcrystalline cellulose (MCC, Comprecel® M 101 D^+, Mingtai Chemical Co., Ltd. Taiwan), zinc chloride ($ZnCl_2$) and calcium chloride ($CaCl_2$) (Merck, Germany) were used as extrusion-spheronization aid and crosslinking agent.

β-cyclodextrin, acetyl-β-cyclodextrin and triacetyl-β-cyclodextrin (Sigma-Aldrich, Germany) were used as additives in the polymer coating.

2.2 Spheroids preparation

Pectinate spheroids were produced by means of extrusion-spheronization process with binding liquid type, and pectin/MCC weight ratio varied (Table 1). The pectin/MCC ratios and binding liquids were selected based on preliminary experiments and literature reports to achieve suitable spheroid formation and mechanical strength. MCC was included as a spheronization aid, and varying the pectin/MCC ratios (3:7, 4:6, and 6:4) allowed assessment of the effect of polymer content on spheroid integrity and drug release. Accordingly, formulations F1–F5 were designed to compare the impact of pectin proportion and the type of binding liquid on spheroid characteristics, enabling systematic identification of an optimal matrix composition for subsequent coating and release studies.

2.5% w/w of 5-FU was used in all batches of formulation. The total amount of powder mass for each batch of formulation was kept at 20 g. Deionized water and aqueous solutions of $ZnCl_2$ and $CaCl_2$ at the respective concentrations of 0.46% w/w and 0.50% w/w were used as binding liquid. The latter contained the same mole of cationic species.

The dry powder blend of pectin, MCC and 5-FU was first pre-mixed for 5 min using mortar and pestle, followed by gradual wetting by a specified amount of binding liquid in a dropwise manner to produce sufficiently plastic wet mass. The duration of mixing and wetting was kept at 30 min. The resultant wet mass was extruded through sieve perforations of 1 mm (Retsch, Retsch GmbH, Germany).

The extrudates formed were spheronized using a mini spheronizer (mini spinner, SAS Safety Auto Sdn Bhd Malaysia) with a rotating plate of regular crosshatch geometry at different speeds and for different processing times. The spheroids were then collected and dried in an oven at 40 ± 0.5°C for 3 days and subsequently equilibrated to a constant weight by storing in a desiccator at 25 ± 0.5°C. Blank spheroids were similarly prepared except that no drug was incorporated.

2.3 Coating formulation

Unless otherwise stated, the coating formulation of spheroids was constituted of 2% w/w pectin and 30% w/w EC dispersed in aqueous solution. A total of 0 to 40% w/w TEC, calculated with reference to unplasticized dry mass, was added when needed (30). The dry weight ratio of pectin to EC in spheroid coat could vary between 1:5

Table 1: Formulation and processing profiles of pectinate spheroids.

	F1	**F2**	**F3**	**F4**	**F5**
Pectin/MCC ratio	3:7	4:6	6:4	4:6	6:4
Granulating liquid amount (g):					
0.50% w/w $CaCl_2$	N/A	13	13	N/A	N/A
0.46% w/w $ZnCl_2$	N/A	N/A	N/A	13	13
Deionized water	13	N/A	N/A	N/A	N/A
Spheronization speed (rpm)	2300	2500	2500	2500	2500
Spheronization time (min)	30	10	10	10	10

and 1:20. Three types of cyclodextrin such as β-cyclodextrin, acetyl β-cyclodextrin and triacetyl β-cyclodextrin were added as additives of coating formulations by means of the following methods:

Method 1
Both pectin and cyclodextrin were dissolved separately in deionized water and added to the dispersion of EC and TEC under magnetic stirring at a speed of 1000 rpm for 30 min.

Method 2
Both pectin and cyclodextrin were dissolved together in deionized water and added into the dispersion of EC and TEC under magnetic stirring at a speed of 1000 rpm for 30 min. The dry weight ratio of pectin, cyclodextrin and EC could vary from 0.5:0.5:10 to 1:1:10.

Two coating approaches were evaluated in order to compare the effect of different preparation strategies on coating uniformity and excipient interaction. In Method 1, pectin and cyclodextrin were dissolved separately in deionized water prior to addition into the EC/TEC dispersion, allowing each component to hydrate individually and minimizing premature interaction. In Method 2, both pectin and cyclodextrin were dissolved together before incorporation into the EC/TEC dispersion, promoting pre-complexation between the two hydrophilic polymers. This comparison was intended to determine whether independent dissolution or combined dissolution would yield superior coating characteristics and influence subsequent drug release behavior.

2.4 Coating process

Five g of pectin core spheroids of sizes ≥ 0.71 mm and < 1.00 mm were placed in a fluid-bed coater (Mini Coater/Drier 2, Caleva, UK) equipped with a top spray coating system (31). One, two and three-gram of coating materials were sprayed with the aim of achieving theoretical coating levels of 20, 40 and 60% w/w of the pectin cores. The coating was conducted in a single or divided runs. The latter was practiced with the aim to reduce excessive core spheroid hydration when necessary. The actual total spheroid coat weight gain after coating was calculated using the following equations:

$$\text{Total spheroid coat weight gain} = \frac{w_2 - w_1}{w_1} \times 100\%$$

Where w_1 is the dry weight of uncoated spheroids and w_2 is the dry weight of coated spheroids. The operational conditions for fluid-bed coating were as follows: agitator vibration rate = 16 Hz; fluidizing air flow rate = 9 m/s; fluidizing air temperature = 45°C; liquid feed rate = 5.3 g/min; atomizing air pressure = 1.5 bar.

The resultant coated spheroids were dried in the same process at 45°C for 10 min upon completion of coating liquid addition. They were further dried in an oven at 40°C for 24 h and subsequently equilibrated to a constant weight by storing in desiccators for at least 5 days prior to physicochemical characterization.

2.5 Drug release and drug content

The drug release profile of spheroids was determined at 37.0 ± 0.2°C under a sink condition. USP buffer pH 2.2 and 6.8 were used as a dissolution medium to simulate the gastric fluid which represented the first entry site of spheroids upon oral administration and intestinal medium respectively. An accurately weighed amount of spheroids at 300 mg was placed in 500 mL of dissolution medium and was agitated at 50 strokes/min in

a shaker bath (ST402, Nuve, Turkey). Aliquots were withdrawn at specific intervals up to 2 h and subjected to spectrophotometric assay using UV-VIS spectrophotometer (Cary 50 Conc, Varian Australia Pty. Ltd., Australia) at the wavelength maxima of 265 nm for 5-FU. The percentage of drug release was calculated with respect to the drug content of spheroids. The drug content was determined by subjecting the same sample of spheroids from the drug dissolution study for an additional 17 h of magnetic stirring followed by ultrasonication for at least five consecutive periods of 5 min each before assaying for 5-FU. Each experiment was carried out in triplicates and the results averaged. Blank spheroids were taken as control sample.

2.6 Coating material aggregation test

Mixing of coating materials in deionized water may lead to formation of solid aggregates. The aggregation tendency of coating materials was examined through mixing of:

a. 2% w/w pectin with 30% w/w EC.
b. 30% w/w EC with 20% w/w TEC.
c. 2 % w/w pectin with 30% w/w EC and 20% w/w TEC.
d. 1% w/w cyclodextrin with 1% w/w pectin and 30% w/w EC.
e. 1% w/w cyclodextrin with 1% w/w pectin, 30% w/w EC and 20% w/w TEC.

Similar tests were conducted on coating formulations prepared by methods 1 and 2 as described under section 2.3 with reference to cases where the dry weight ratio of coating materials pectin, cyclodextrin and EC was 0.5:0.5:10. The solid aggregates formed were first harvested wet through using a nest of standard sieves between 500 µm and 2000 µm. The collected aggregates were then dried in an oven at 40°C for one day with weight characterized thereafter. Triplicates were conducted and the results averaged.

2.7 Morphology study

The surface morphology of spheroids was examined using the SEM technique (JSM-6360LA, JEOL, Japan). The spheroids are first fixed with a carbon tape onto the aluminium stud and sputter-coated with a thin gold-palladium layer (JFC-1600, Jeol, Japan) prior to viewing directly under a scanning electron microscope at a magnification level up to 20000 ×. Representative sections were photographed.

2.8 Fourier transform infrared (FTIR) spectroscopy

A mixture of sample material with dry potassium bromide, at a weight ratio of 2:78, was finely powdered using an agate mortar. The resulting powder was compressed into a disc, which was then scanned across a wavenumber range of 400 to 4000 cm^{-1} using the FTIR spectrometer (Spectrum RX1 FTIR system, Perkin Elmer, USA) at a resolution of 4 cm^{-1}. Triplicate measurements were performed, and the results were averaged.

2.9 Coat composition

The coat composition of spheroids, obtained from drug dissolution process following coat detachment from the pectin core, was analysed using infrared spectroscopy. The detached coat obtained during drug dissolution was mainly constituted of EC as pectin was lost through solubilization in the aqueous medium.

2.10 Statistical Analysis

All data were expressed as a mean of at least three experiments with the corresponding standard deviation. One-way analysis of

variance (ANOVA)/post hoc comparison between groups with Tukey multiple-comparison test was employed when applicable. Statistical analysis was carried out using SPSS Statistics software version 22.0 (IBMCorp., USA) and statistically significant differences were denoted by $p < 0.05$ where applicable.

3.0 Results and discussion

3.1 Preparation of spheroids

Spheroids of low pectin/MCC ratio at 3:7 can be prepared without the use of crosslinking agent as a part of the binding liquid component (F1). In the case of using higher pectin/MCC ratios such as 4:6 and 6:4, mere deionized water as binding liquid led to the formation of rod-shaped spheroids (Fig. 1Ia). The extrudates of such formulations were cohesive and resisted spheronization even at high speeds of 1500 to 2500 rpm for a maximum duration of 30 min. Reducing the binding liquid quantity from 13 to 11g resulted in failure to produce coherent extrudates (Fig. 1Ib). The formed extrudates exhibited sharkskin-like appearance. This gave rise to the formation of rod-shaped spheroids with small and large diameters, where the small particles were entities detached from the large counterparts (Fig. 1Ic).

Pectin is a water-soluble polysaccharide (32). Wetting of pectin by water led to immediate hydration, swelling and an increase in adhesiveness of the powder mass thereby resulting in strong binding of particles in extrudates and failure of mass to be spheronized. Pectin is a polymer constituted of polygalacturonic acid as the main backbone (33-35). It can be crosslinked by multivalent cations such as soluble Ca^{2+} and Zn^{2+} (36,37). Crosslinking of pectin chains by divalent cation has been reported to be able to increase the rigidity of the solid matrix (38). It aids the extrudates to break down under the rotational forces of friction plate and spheronize into round particles.

Preliminary studies of the present investigation found that both soluble Ca^{2+} and Zn^{2+} were suitable for use as extrusion and spheronization aid, when friction plate characterized by grooved surface with large pyramidally-shaped elevations or square studs and had higher levels of shearing forces was used. The combination of crosslinking agent and high shearing forces imparted by the crosshatched pattern of friction plate formed the prerequisite to succeed in spheroid formation (Fig. 1Id).

3.2 Drug release

3.2.1 Uncoated spheroids

Drug release of uncoated spheroids was analysed using buffer USP pH 2.2 and 6.8 to simulate gastric and intestinal media. Overall, the addition of calcium or zinc salt into spheroids resulted in lower release profiles of 5-FU (Fig. 2a and b). In pH 2.2 buffer medium, zinc pectinate spheroids prepared from 6:4 weight ratio of pectin to MCC (F5) demonstrated the lowest extent of drug release (Fig. 2a; ANOVA: $p < 0.05$). Zinc pectinate spheroids produced using 4:6 weight ratio of pectin to MCC (F4) had similar drug release profiles to that of calcium pectinate spheroids formulated using the same weight ratio of pectin to MCC (F2) (Fig. 2a; ANOVA: $p > 0.05$). With reference to zinc pectinate spheroids produced using 6:4 weight ratio of pectin to MCC, calcium pectinate spheroids of the same pectin/MCC content (F3) experienced a faster drug release

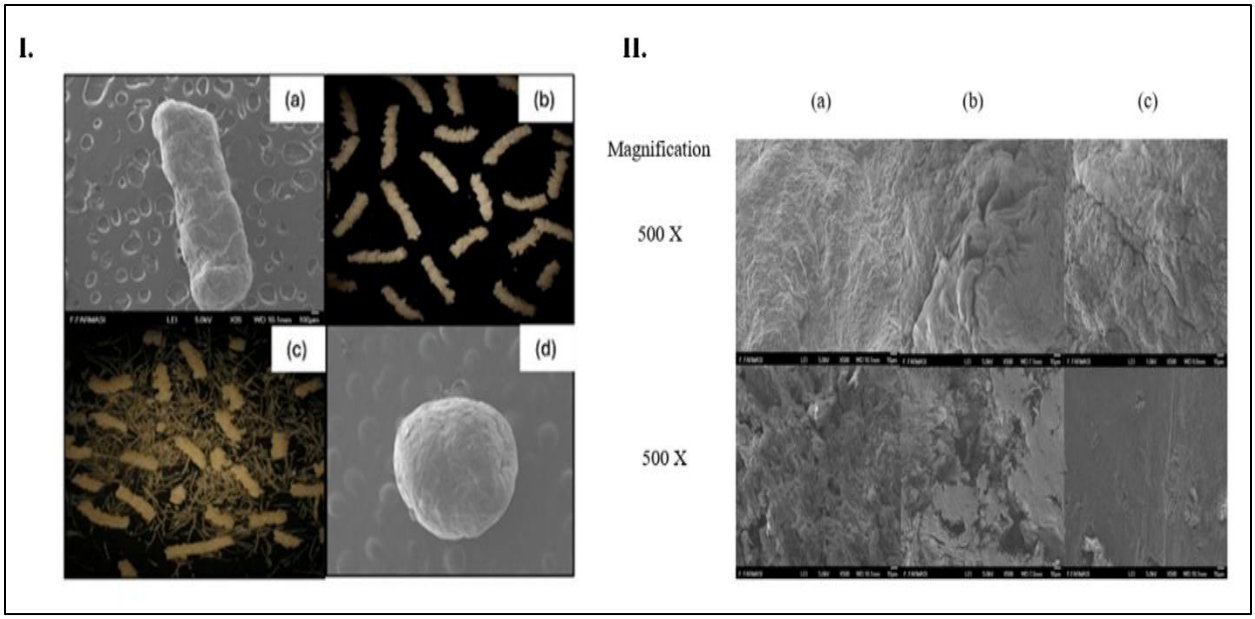


Fig.1: I. SEM image of (a) pectin core spheroids with deionized water as the binding liquid (magnification: 35X), (b) sample of extrudates (magnification: 5X), (c) powdery rod-shaped spheroids (magnification: 5X) and (d) pectin core spheroids with a crosslinking agent as the binding liquid (magnification: 55X) and II. Surface and cross-sectional morphologies of (a) non-crosslinked, (b) calcium and (c) zinc crosslinked pectinate spheroids.

than samples formulated using a lower pectin to MCC weight ratio (Fig. 2a).

Theoretically, calcium or zinc salt loaded matrices prepared with a high pectin-to-MCC weight ratio were expected to exhibit fast drug release due to a low crosslinking density. Nonetheless, such phenomenon was not observed in the case of zinc pectinate spheroids. Compared to Ca^{2+}, Zn^{2+} are able to produce stronger pectinate network and showed improved stability in the upper gastro-intestinal tract and slower drug release (39). Zn^{2+} interact with both the carboxyl and the hydroxyl groups of pectin, while Ca^{2+} interact only with carboxyl groups resulting in galacturonate chains that are more loosely associated with each other in the presence of Ca^{2+} than with Zn^{2+}(40). Fig. 1II shows Zn^{2+} induced more extensive crosslinking between pectin chains than Ca^{2+}. A greater proportion of pectin was involved in crosslinking process of Zn^{2+} in F5 throughout its inner core bed inferring from the dense microstructure of matrix. This could probably explain its sustained drug release attribute (Fig. 2a).

With reference to the positive sustained-release profiles, F2, F4 and F5 were subjected to further drug release analysis in buffer USP pH 6.8 (Fig. 2b). At the same pectin to MCC weight ratio of 4:6, zinc pectinate spheroids F4 demonstrated a low level of drug release in comparison to calcium pectinate spheroids F2. Zinc pectinate spheroids F5 which was characterized by high pectin to MCC weight ratio gave an unexpectedly fast drug release.

In buffer pH 6.8, a greater exchange of Zn^{2+} at pectin crosslinkages with Na^{+} and K^{+}, and sequestration of Zn^{2+} by PO_4^{3-} of buffer could possibly reduce the crosslinking density of the majority of pectin in zinc pectinate spheroids F5. Such observation could be ascribed to weaker matrix interaction at C=O regime (wavelength range 1650-1800 cm^{-1}) of F5 spheroids when compared to F2 and F4 spheroids, as

indicated by larger wavenumber and lower transmission intensity of the FTIR bond (Fig. 3I). This in turn led to fast drug release. The drug release of pectinate spheroids was generally faster in buffer USP pH 6.8 than pH 2.2. In buffer pH 6.8, the carboxylic acid molecules of pectin were ionized through deprotonation. Repulsion between the ionized pectin chains could lead to porous matrix formation and facilitate drug release.

3.2.2 Coated spheroids

Since the F4 zinc pectinate spheroids exhibited low drug release in both simulated gastric and intestinal media, further studies on spheroid coating and drug release were carried out using F4 spheroids as the matrix of interest.

Table 2 shows the surface and cross-sectional morphologies of uncoated and coated F4 spheroids. Coating of spheroids by EC and pectin mixture plasticized with TEC was accompanied by particulate deposition and coalescence at the surfaces of core matrix. This led to core spheroids encapsulated by a shell.

In preliminary trials, fluid-bed coating of multi-particulate pectin core spheroids was accompanied by low coat weight gain (experimental: 0.30 ± 0.13 g, 0.35 ± 0.14 g and 0.44 ± 0.22 g coat/5 g spheroids; 30%, 17.5% and 14.6% of theoretical target coat weight) due to losses of coating material from spheroids onto wall of processor during coating thereby leading to inadequate retardation of 5-FU release in simulated gastric medium which represented the first site of spheroid entry in gastrointestinal tract (Table 3).

The propensity of 5-FU release was high at various plasticizer levels and pectin:EC weight ratios. It was not adequately retarded in spite of larger quantities of coating materials were used and coating materials were sprayed in multiple steps instead of in a continuous run or from a more concentrated liquid system to avoid excessive core hydration which hindered hydrophobic coating and translated to coat detachment during dissolution. The loss of EC as drug release retardant was verified by FTIR analysis of the detached coat (Fig. 3II). The characteristic FTIR peaks of unprocessed EC at 2875.5 ± 0.2 and 2977.4 ± 0.3 cm^{-1} were noted in spectra of leached substances collected from dissolution medium. Leaching of the pectin component, and the subsequent detachment of the EC coat, was one of the primary factors giving rise to poor drug release control.

3.3 Cyclodextrin as coating materials

Cyclodextrins is mainly sub-divided into three types-based glucose amounts: α-cyclodextrins (6 glucose molecules), β-cyclodextrins (7 glucose molecules) and γ-cyclodextrins (8 glucose molecules) (41-44). β-cyclodextrin is currently the most common cyclodextrin in pharmaceutical applications and probably the best studied cyclodextrin in humans (45-47). With the substitution of acetyl moiety, the hydrophobicity of cyclodextrins increases and this is expected to aid drug release retardation (48,49). Replacing of a part of pectin with cyclodextrin was envisaged to be able to negate fast drug release attribute of spheroids following pectin leaching and EC detachment through its hydrogen bonding with pectin via OH moiety (50) and hydrophobic insertion of EC in cyclodextrin core.

Through substituting 50% of pectin coat with cyclodextrins, drug release studies indicated that β-cyclodextrin was able to reduce the rate and extent of drug dissolution of F4 spheroids (Fig. 2c) (ANOVA: $p<0.05$).

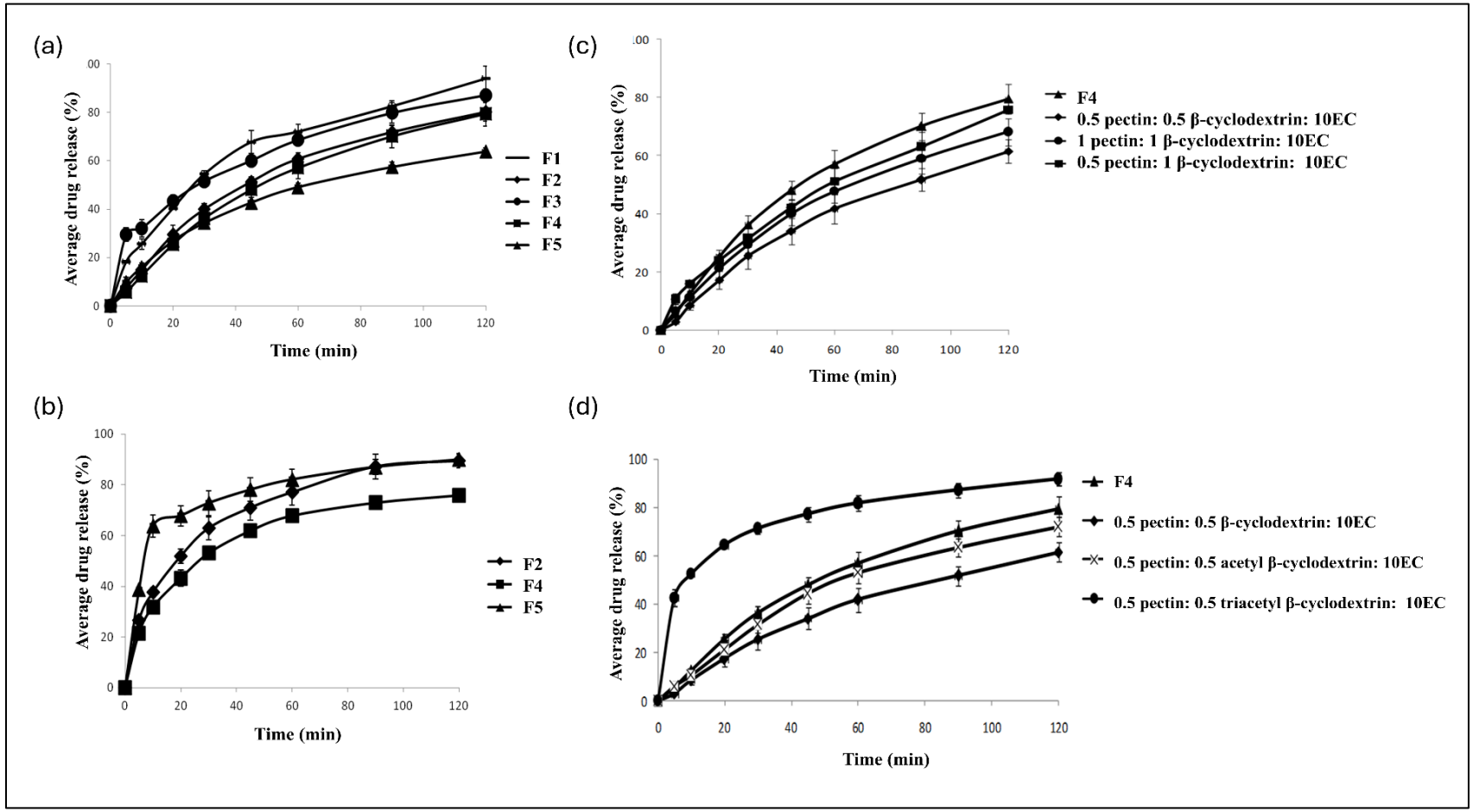


Fig. 2: Drug release profiles of calcium pectinate and zinc pectinate spheroids in buffer (a) pH 2.2, (b) pH 6.8 and spheroids coated with (c) β-cyclodextrins at varying compositions and (d) β-cyclodextrin, acetyl β-cyclodextrin and triacetyl β-cyclodextrin at 0.5 pectin: 0.5 cyclodextrin: 10EC composition in buffer pH 2.2.

Table 2: Surface and cross-sectional morphology of uncoated and coated zinc pectinate spheroids.

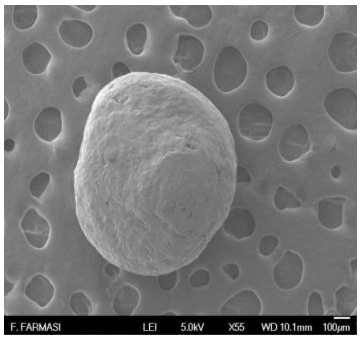
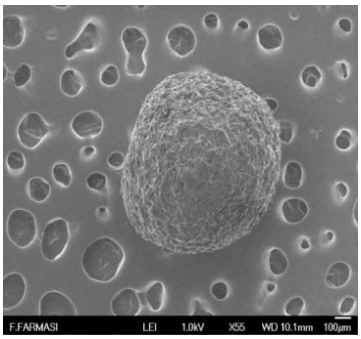
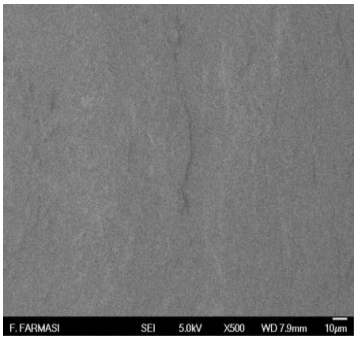
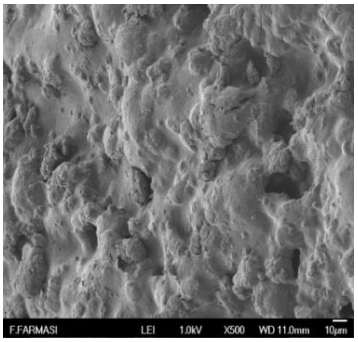
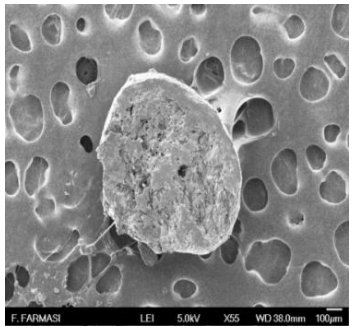
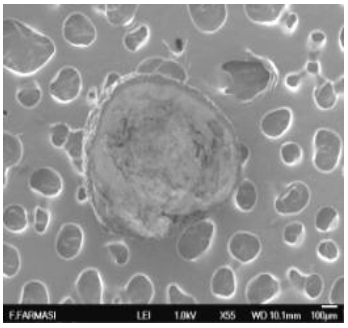
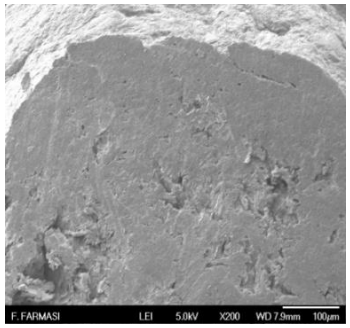
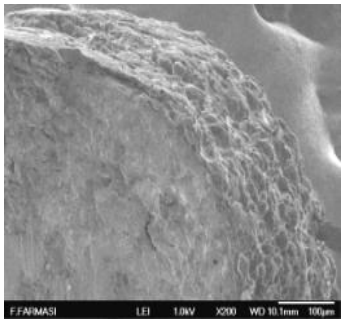
	Uncoated zinc pectinate spheroids	Coated zinc pectinate spheroids
	Surface Morphology	
Magnification: 55X		
Magnification: 500X		
	Cross-sectional morphology	
Magnification: 55X		
Magnification: 200X		

Table 3: Drug release profiles of uncoated spheroids and spheroids coated by EC and pectin mixture by means of fluid-bed film coating technique.

Sample	Drug release in buffer pH 2.2 at 2 h (%)	Sample	Drug release in buffer pH 2.2 at 2 h (%)
Uncoated spheroids	79.5 ± 5.2	1 pectin:20 EC. 20% TEC. 1 g coating material sprayed in 1 run.	93.9 ± 3.9
1 pectin:10 EC. 20% TEC. 1 g coating material sprayed in 1 run.	68.1 ± 4.2	1 pectin:5 EC. 20% TEC. 1 g coating material sprayed in 1 run.	90.8 ± 5.1
1 pectin:10 EC. 20% TEC. 2 g coating material sprayed in 1 run.	87.3 ± 1.7	1 pectin:5 EC. 0% TEC. 1 g coating material sprayed in 1 run.	99.1 ± 3.1
1 pectin:10 EC. 20% TEC. 3 g coating material sprayed in 1 run.	85.4 ± 3.2	1 pectin:10 EC. 40% TEC. 1 g coating material sprayed in 1 run.	89.3 ± 3.3
1 pectin:10 EC. 20% TEC. 3 g coating material sprayed in 3 separate runs.	90.3 ± 0.5	1 pectin:10 EC. 10% TEC. 1 g coating material sprayed in 1 run.	81.2 ± 1.2

Unexpectedly, acetyl substitution negated the drug release retardation effect of cyclodextrin (Fig. 2d). Coated spheroids of triacetyl β-cyclodextrin, the most hydrophobic cyclodextrin of all, exhibited a faster drug release than that of cyclodextrin-free coated spheroids (Fig. 2d).

SEM analysis showed that pectin/EC coat with added β-cyclodextrin via method 1 demonstrated a homogeneous film structure thereby aptly explained its sustained drug release attribute (Fig. 3Ia-d). With the use of acetyl moiety containing cyclodextrins, aggregates of coating materials were found on the surfaces of spheroids. The coating was heterogeneous with uncoated surfaces exposed to the exterior medium. This resulted in fast drug release. The level of coat material aggregation was higher with the use of triacetyl β-cyclodextrin and such spheroids were characterized by an exceedingly fast drug release than that of coated by cyclodextrin-free methods (Fig. 2d). High coating material aggregation was initiated in the presence of triacetyl β-cyclodextrin as hydrophobic interaction between EC and β-cyclodextrin could have promoted by the dense acetyl population in dextrin molecules. In avoidance of excessive EC–cyclodextrin interaction and loss of complexing function of cyclodextrin for both pectin and EC, subsequent studies were conducted with cyclodextrin first added to pectin prior to its introduction into EC/TEC dispersion (method 2). Generally, the coated spheroids exhibited a faster drug release propensity than that of coated with cyclodextrin solution

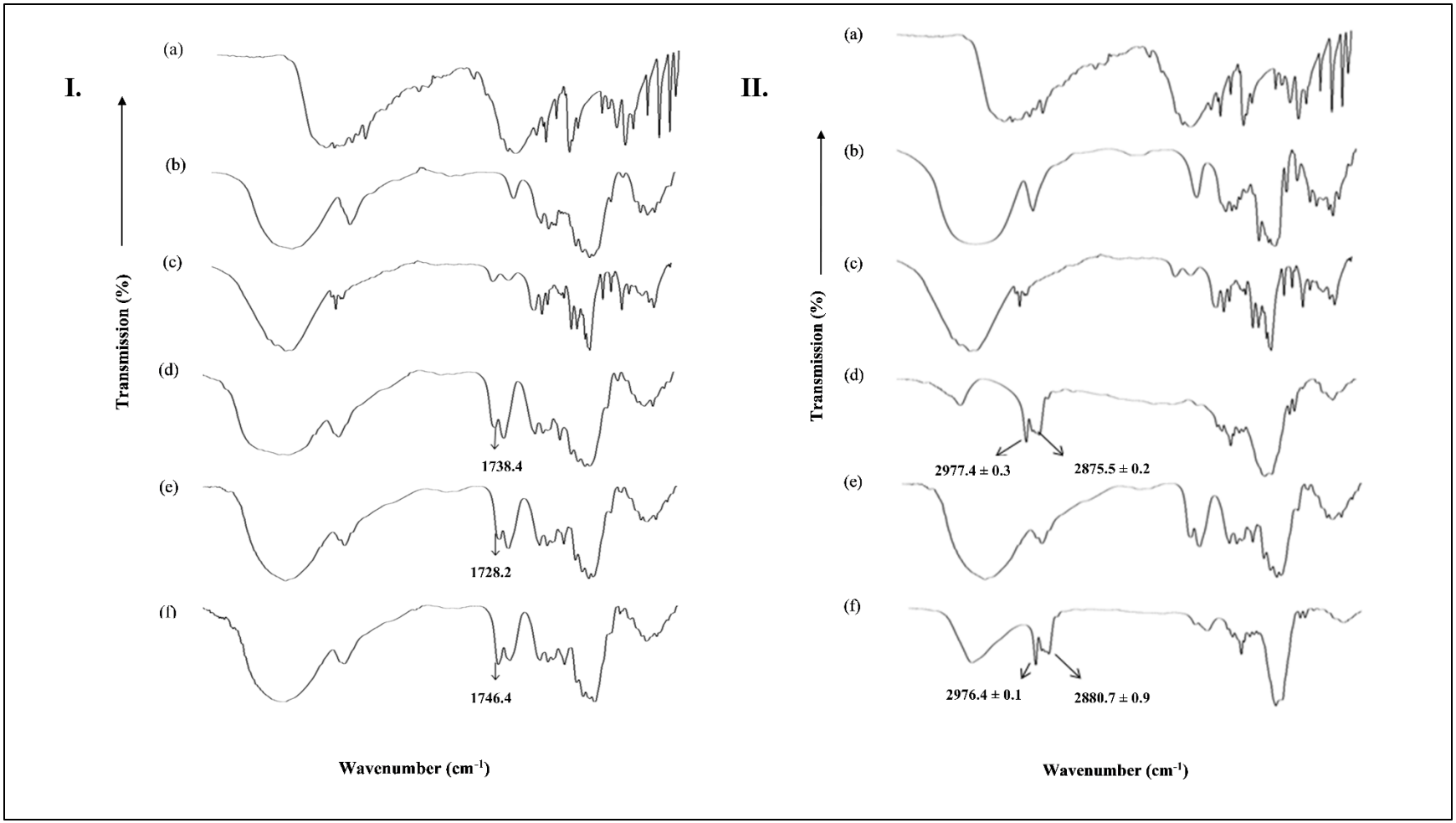


Fig. 3: I. FTIR spectra of (a) 5-FU, (b) MCC, (C) pectin, (d) F2, (e) F4 and (f) F5 spheroids and II. FTIR profiles of (a) 5-FU, (b) MCC, (c) pectin, (d) EC, (e) uncoated spheroids and (f) sample of detached coat obtained during dissolution analysis of spheroids processed by fluid-bed film coating technique.

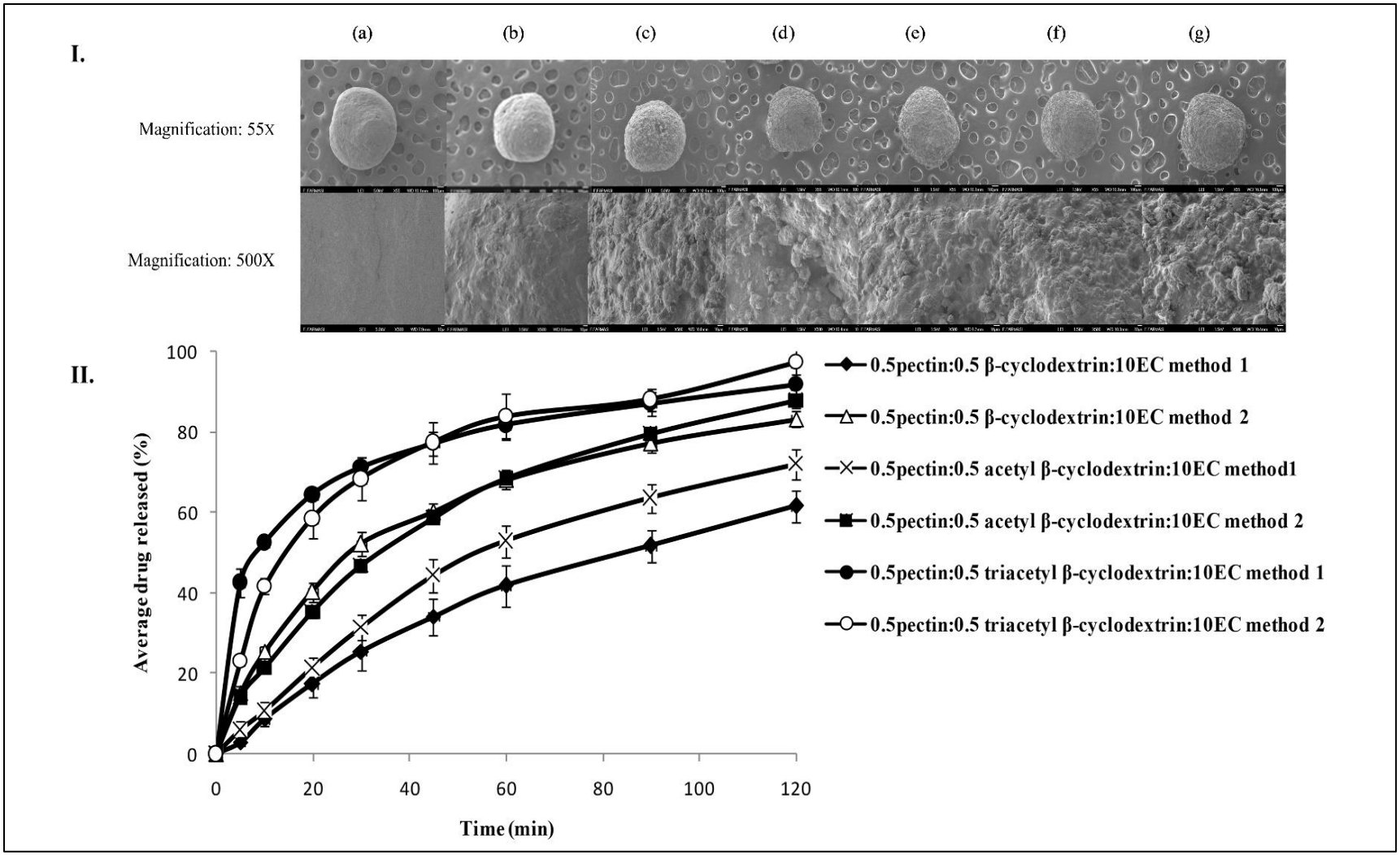


Fig. 4: I. Surface morphology of (a) uncoated F4 spheroids, spheroids coated using coating method 1 with (b) β-cyclodextrin, (c) acetyl β-cyclodextrin and (d) triacetyl β-cyclodextrin as additives, spheroids coated using coating method 2 with (e) β-cyclodextrin, (f) acetyl β-cyclodextrin and (g) triacetyl β-cyclodextrin as additives. II. Drug release of F4 spheroids coated with β-cyclodextrin, acetyl β-cyclodextrin and triacetyl β-cyclodextrin as coating additives by means of different coating mixture preparation methods in buffer pH 2.2.

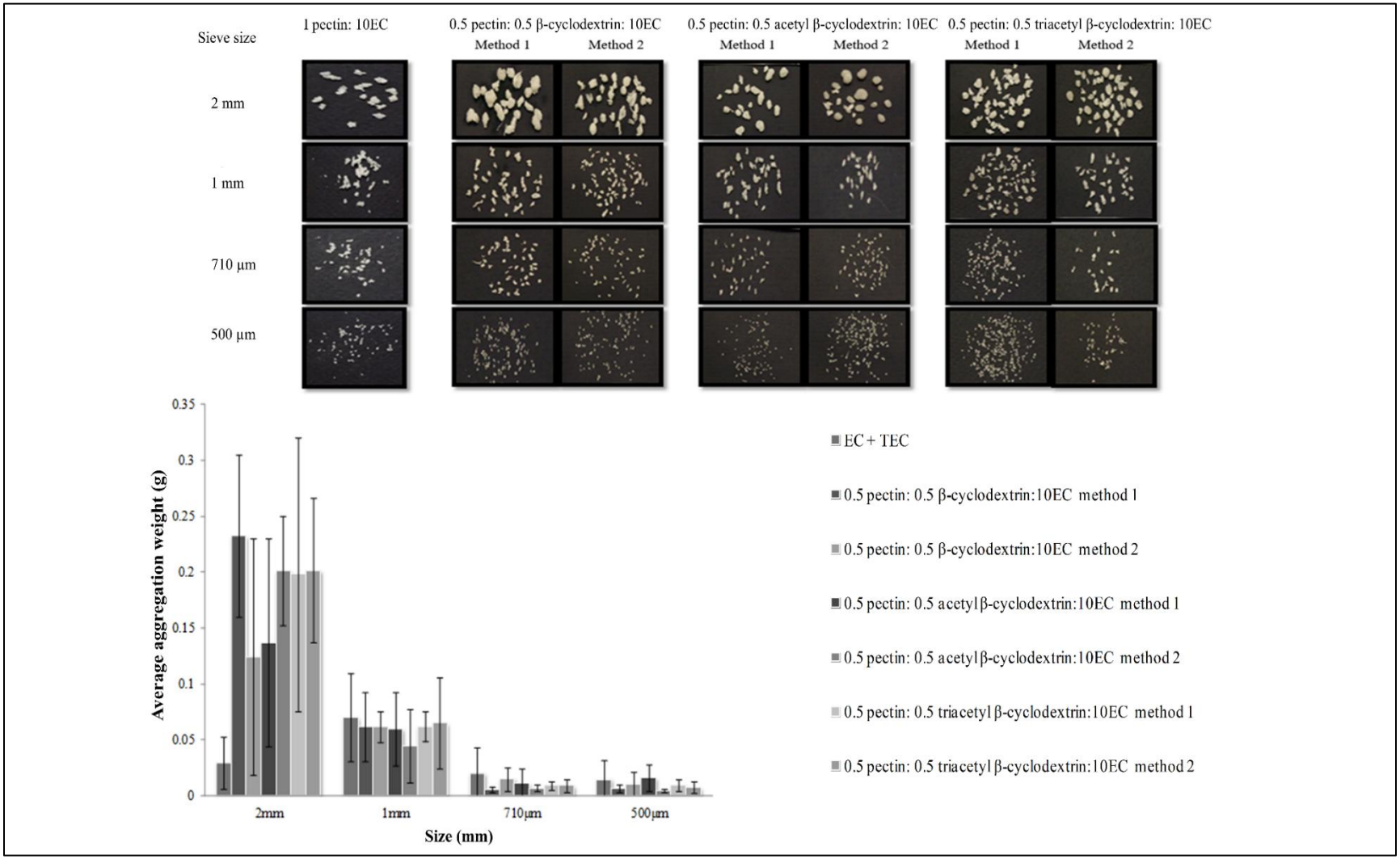


Fig. 5: Aggregation profiles of coating materials.

added separately from pectin solution into EC/TEC dispersion (method 1) (Fig. 4II). However, there was no marked changes in drug release profiles of spheroids coated from triacetyl β-cyclodextrin loaded coating materials. Triacetyl β-cyclodextrin, being hydrophobic, exhibited preferential interaction with EC thereby giving rise to spheroids with surface coat aggregation and fast drug release (Fig. 4Ig). β-cyclodextrin, being the less hydrophobic cyclodextrin of all, appeared to interact preferentially with pectin and has its interaction propensity with EC reduced. The coat structure formed on spheroids was characterized by aggregates streamlining regimes of pectin-β-cyclodextrin and EC/TEC, different from coat prepared with pectin and cyclodextrin solutions added separately into EC/TEC dispersion. The heterogeneous coat structure of these spheroids was translated to fast drug release due to discontinuity of hydrophobic EC protection against early drug release (Fig. 4Ib and e). Similar outcomes were applicable to cases of using acetyl β-cyclodextrin. A pre-mixing of acetyl β-cyclodextrin with pectin could reduce its excessive aggregation with EC on the surfaces of coated spheroids. Nonetheless, this induced pectin-acetyl β-cyclodextrin interaction which in turn hindered continuous EC film formation through the complexation effect of cyclodextrin.

Coating material aggregation was a resultant nature of cyclodextrin molecules, where they can self-assemble or aggregate in aqueous solution and had the ability to interact with the neighbouring substances. Fig. 5 shows the aggregation profiles of coating materials prepared by methods 1 and 2 using cyclodextrin series as additives. Hydrophobic and van der Waals forces are considered as the main driving components in the formation of cyclodextrin aggregates (51). In the absence of cyclodextrin, EC and TEC tend to interact and form small aggregates. Using cyclodextrin, a high degree of aggregation between coating methods took place. Aggregation was promoted by TEC, as it enabled wetting between hydrophilic and hydrophobic excipients that would otherwise not be possible.

5.0 Conclusion

Crosslinking of pectin with Zn^{2+} can aid to retard 5-FU release from the spheroids. Coating of these spheroids by means of pectin-EC mixture was characterized by EC coat detachment and fast drug release. A partial replacement of pectin coat in pectin-EC mixture with β-cyclodextrin further reduced the propensity of drug release. This was attributed to low aqueous solubility of β-cyclodextrin and its ability to interact with both pectin and EC in coat to form continuous drug release barrier. Using acetyl containing cyclodextrin series as coat additive, unexpectedly fast drug release was noted from zinc pectinate spheroids. Hydrophobic part of cyclodextrin exhibited preferential binding to EC. It gave rise to different coat domains from pectin and discontinuity in drug release barrier thereby prompting fast drug release.

Authorship contribution statement

NAL: Formal analysis, Investigation, Writing – original draft; **AI**: Visualization, Writing – review & editing; **IN**: Investigation

Acknowledgment

The authors would like to express their gratitude to Prof Dr Wong Tin Wui, SMRI; Faculty of Pharmacy, UiTM Puncak Alam Campus for providing support and guidance in the making of this research article.

Conflict of Interest

The authors declared that they have no conflicts of interest to disclose.

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