Theophylline-Loaded Pectin/Chitosan Hydrochloride Submicron Particles Prepared by Spray Drying with a Continuous Feeding Ultrasonic Atomizer

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Abstract: Pectin/chitosan hydrochloride (CHC) particles containing theophylline were prepared by a spray-drying apparatus coupled with a continuous feeding ultrasonic atomizer and a heating column. The formation of the submicron particles was investigated at various compositions of pectin solutions added with a chitosan hydrochloride or calcium chloride solution as a crosslinking agent. Scanning electron microscopic (SEM) images showed the pectin/chitosan hydrochloride particles had spherical and smooth surfaces. Depending on the feeding concentrations, the produced particles had diameters in the range of 300 to 800 nm with a narrow size distribution. Furthermore, the theophylline (TH)-loaded pectin/CHC particles were also prepared by the same apparatus. The TH release from the submicron particles in phosphate-buffered saline at 37 °C was monitored in real-time by a UV-Visible spectrophotometer. The Ritger–Peppas model could well describe the TH release profiles. All the diffusional exponents (n) of the release systems were greater than 0.7; thus, the transport mechanism was not a simple Fickian diffusion. Particularly, the

Keywords: pectin; chitosan hydrochloride; submicron particles; ultrasonic atomizer; spray dryer; Ritger–Peppas model; control release

1. Introduction

Pectin is a natural anionic hetero-polysaccharide in many terrestrial plants’ cells (Scheme 1). It is mainly extracted from citrus fruit peel for applications in many food products, such as jellies, jams, and dietary fiber. Furthermore, pectin can be used in the pharmaceutical field owing to its good biocompatibility [1–3]. For example, pectin can be crosslinked with calcium ions, which is a suitable delivery system to escort drugs from the mouth to the colon [4,5]. On the other hand, chitosan and chitosan hydrochloride chitosan (Scheme 2) are cationic polysaccharide polymer derived from chitin, which can be found in the shells of shrimp, crabs, lobsters, etc. Chitosan can be used as a drug carrier because of its good mucoadhesive and anti-inflammatory properties. A polyelectrolyte complex of pectin and chitosan can be primarily formed by ionic interactions between the ionized carboxyl acid groups of pectin and amino groups of chitosan [6–11]. For example, vancomycin-loaded pectin/chitosan complex tablets had good mucoadhesive properties and a pH-dependent swelling sensitivity for colon delivery [8]. The anti-Alzheimer was encapsulated in chitosan/pectin microparticles of approximately 2 to 20 µm in diameter for nasal administration of tacrine hydrochloride [11].
Many submicron polymeric particles as drug carriers have exhibited excellent physicochemical properties and could overcome the biological barriers to delivering the loaded drug to the target site [12–20]. Resveratrol-loaded chitosan/pectin nanoparticles were prepared by using a complicated process including antisolvent precipitation and electrostatic deposition methods, and the complex particles could entrap resveratrol for a longer time [21]. Theophylline (TH, Scheme 3) can be used for treating asthma and chronic obstructive pulmonary illnesses [22,23]. In the previous study, we demonstrated a simple spray-drying process to produce theophylline (TH)-loaded chitosan submicron particles [24]. The drops were produced by ultrasonic atomization from a mixture solution of chitosan, TH, and tripolyphosphate (TPP) in a conical flask, then dried in a heating column. However, as the initial precursor solution contained the crosslinking agent TPP, most chitosan was crosslinked with TPP before being atomized. Therefore, the crosslinking density of the spray-dried particles would be varied at different collecting times.

In this study, a modified spray drier coupled with two continuous feeding streams was set up. One stream contained a pectin solution, and the other one was filled with a crosslinker solution. They were then mixed and the formation of particles was investigated at various compositions of the pectin, chitosan hydrochloride, and theophylline (TH) in the aqueous solution. The new continuous feeding process could keep the concentration and composition of the precursor solution at a constant condition, and reduce the crosslinking reaction before spray drying. First, the pectin particles with the CHC were prepared at various concentrations of the feeding precursor solutions. The size and morphology of the spray-dried pectin/CHC particles were observed using a scanning electron microscope (SEM). The hydrodynamic diameters of the particles in the PBS were measured by using a dynamic light scattering (DLS) method. Theophylline (TH)-loaded pectin particles with a crosslinking agent, such as CHC or calcium chloride, were further fabricated by the twin-syringe, continuous-feeding ultrasonic atomizer. The TH release from the pectin/CHC particles was monitored and compared.

Scheme 1. Pectin.

Scheme 2. Chitosan hydrochloride.

Scheme 3. Theophylline.
particles in PBS was monitored using real-time UV-Visible spectroscopy. Finally, a release kinetic model was proposed to describe the drug release mechanism.

2. Materials and Methods

2.1. Materials

Pectin extracted from citrus with a molecular weight of approximately 20–40 kDa was purchased from Tokyo Chemical Industry (Tokyo, Japan). Chitosan hydrochloride (CHC) was obtained from Charming & Beauty Co., Ltd. (Taipei, Taiwan). Calcium chloride (CaCl$_2$) was provided by Showa Chemical Industry (Tokyo, Japan). Theophylline (TH) was purchased from Acros Organics (Geel, Belgium), which was used as a model drug.

2.2. Preparation of Pectin/Chitosan Hydrochloride Microparticles

A homemade spray drier was set up using an ultrasonic atomizer with a continuous multiple feeding syringe pump and coupled with a heating column as shown in Figure 1. An aqueous pectin solution (0.05–0.15 mg/mL, coded as A) with or without theophylline (TH, 0.2 mg/mL) was filled into a syringe, and another aqueous solution containing CHC (0.1, 0.2 mg/mL) or calcium chloride (0.10 mg/mL) as a crosslinking agent (coded as B) was filled into the other syringe. These two solutions, A and B, were then fed into the atomizer cell at a constant flow rate of 0.125 mL/min by a syringe pump (NE-4000, NEW ERA Pump Systems Inc., Farmingdale, NY, USA). The spray drops of the mixed solution would float and be dried in a heated upstream airflow under 1.6 L/min. at controlled temperatures of $T_1 = 130^\circ$C; $T_2 = 140^\circ$C; and $T_3 = 150^\circ$C. The dried particles were collected by a polytetrafluoroethylene membrane (MPT2247, 0.22 µm, ChromTech, Bad Camberg, Germany) and kept in a dry box for further study.

![Spray drying apparatus](image_url)

**Figure 1.** Spray drying apparatus coupled with a continuous-feeding ultrasonic atomizer, in which $T_1$, $T_2$ and $T_3$ indicated the temperatures measured by thermocouples.

2.3. Characteristics of Pectin/Chitosan Hydrochloride Microparticles

For the morphology observation, the prepared particles were first sputter-coated with Au/Pd; then, the coated particles were observed by scanning electron microscopy (SEM, HITACHI S-3000H, Tokyo, Japan) at an accelerating voltage of 5 kV. Particle sizes and zeta potential of the spray-dried samples in phosphate-buffered saline (PBS, pH
6.8) at 37 °C were also analyzed by using the dynamic light scattering method (Nano Series, Malvern Panalytical Ltd., Almelo, Netherlands). Attenuated total reflection–Fourier transform infrared spectroscopy (ATR-FTIR, Spectrum 3, PerkinElmer, Waltham, MA, USA) was performed at room temperature in the range between 500–4000 cm⁻¹ to detect the functional groups of the prepared particles.

2.4. The Release Profile of TH from the Prepared Pectin/Chitosan Hydrochloride Microparticles

5 mg of TH-loaded pectin/CHC microparticles was suspended in 0.5 mL of PBS (pH 6.8), and the solution was placed in a dialysis sack (Cellu.Sep T1, MWCO = 3500, Membrane Filtration Product, Inc., Seguin, TX, USA). The sack was further introduced into a release medium of 100 mL PBS, which was stirred at 100 rpm under 37 °C. The TH released into the buffer solution was measured by a UV-Visible spectrophotometer coupled with a dip probe (TP300-UV-VIS, Ocean Optics, Orlando, FL, USA) under real-time monitoring. The concentration of TH was determined by measuring the light absorbance at a wavelength of 272 nm with the help of a calibration curve constructed from the standard solutions of TH. By using that releasing test, the experimental drug loading contents (LC, %), and the encapsulation efficiency (EE, %) of the TH-loaded particles can be determined by the following equations:

\[
\text{LC} \, (\%) = \frac{\text{mass of drug in particles}}{\text{mass of particles}} \times 100 \quad (1)
\]

\[
\text{EE} \, (\%) = \frac{\text{experimental drug loading}}{\text{nominal drug loading}} \times 100 \quad (2)
\]

where the mass of the drug in the TH-loaded particles was estimated by the measured concentration of TH after releasing for three hours, and the nominal drug loading was calculated by the mass fraction of TH in the solid content of the fed precursor solution.

3. Results and Discussions

3.1. Characteristics of Pectin/Chitosan Hydrochloride Microparticles

The morphology and particle size distribution of the spray-dried pectin/CHC complex particles prepared by the continuous-feeding solutions of the pectin with the CHC were observed by using the SEM as shown in Figure 2. Most of the pectin/CHC particles formed under drying at controlled temperatures: \(T_1 = 130 ^\circ\text{C}; T_2 = 140 ^\circ\text{C};\) and \(T_3 = 150 ^\circ\text{C},\) had smooth surfaces and spherical shapes. Because the atomized drop contained higher solid content at a higher precursor concentration in the feeding solution, the size of the dried particles was expected to be larger once the water had been vaporized. The number average diameter size, \(D_n,\) of the pectin/CHC particle calculated by the SEM thus increased with the increase in the precursor concentration as shown in Table 1 and Figure 3. For example, The \(D_n\) was approximately 294 nm for the particles made from the solutions of pectin and CHC at concentrations of 0.05 and 0.01 mg/mL (sample PC0), respectively. It was increased to 788 nm as the concentrations of pectin and CHC were increased to 1.5 and 0.3 mg/mL (PC5), respectively. The diversity of the particle size was usually described by the geometric standard deviation (G.S.D.) [24]. The G.S.D. value was 1.52 of the pectin/CHC made from the precursor solution with 0.3 mg/mL of the pectin and 0.06 mg/mL of the CHC (sample PC2). However, the values of the other samples were less than 1.4. It implies that the pectin/CHC submicron particles with a narrow particle size distribution can be prepared by using the continuous-feeding ultrasonic atomizer coupled with a heating column in the spray drier.
Table 1. Mean particle size ($D_n$, $D_{VM}$) and particle size distribution (G.S.D.) of pectin/CHC particles measured by SEM images.

| Sample | Pectin (mg/mL) | CHC (mg/mL) | $D_n$ (nm) | $D_{VM}$ (nm) | G.S.D. |
|--------|----------------|-------------|------------|---------------|--------|
| PC0    | 0.05           | 0.01        | 294 ± 73   | 296 ± 95      | 1.38   |
| PC1    | 0.1            | 0.02        | 389 ± 72   | 384 ± 127     | 1.25   |
| PC2    | 0.3            | 0.06        | 467 ± 176  | 485 ± 144     | 1.52   |
| PC3    | 0.5            | 0.1         | 566 ± 115  | 557 ± 176     | 1.31   |
| PC4    | 1              | 0.2         | 691 ± 177  | 645 ± 191     | 1.19   |
| PC5    | 1.5            | 0.3         | 788 ± 214  | 763 ± 225     | 1.31   |

$D_n$: number average particle diameter; $D_{VM}$: volume mean diameter; G.S.D.: geometry standard deviation [24].

Figure 2. SEM images and corresponding particle size distributions of the pectin/CHC particles (PC0 to PC5) prepared from various solutions of pectin and CHC at different compositions.

Figure 3. Variation in number average particle size ($D_n$) of the spray-dried pectin/CHC particles with the pectin concentration, in which the weight ratio of pectin and CHC was kept at 5:1 as indicated in Table 1.
3.2. Characteristics of Theophylline-Loaded Pectin Particles

In this study, theophylline (TH) was selected as a model drug that was added to the pectin solution at a concentration of 0.2 mg/mL. The TH-loaded pectin particles were fabricated by adding two different crosslinking agents in another solution, namely, a high-molecular-weight cationic polysaccharide of CHC and a cationic ion of Ca$^{2+}$ for comparison. They were prepared under the same processing conditions as mentioned above. According to the SEM observation, as shown in Figure 4, the TH-loaded pectin particles exhibited a smooth surface and spherical structure, which was similar to that without the addition of TH. When the feeding concentrations of the pectin and TH were, respectively, 0.5 and 0.2 mg/mL, the $D_n$ of the pectin particles containing TH, sample PT0, was approximately 553 nm as indicated in Table 2.

Table 2. Mean particle size ($D_n$, $D_{VM}$), particle size distribution (G.S.D.), loading content (LC), and encapsulation efficiency (EE) of the TH-loaded pectin particles (concentration of TH = 0.2 mg/mL).

| Sample | Pectin (mg/mL) | CHC (mg/mL) | CaCl$^2$ (mg/mL) | $D_n$ (nm) | $D_{VM}$ (nm) | G.S.D. | Zeta Potential (mV) | LC (%) | EE (%) |
|--------|----------------|-------------|-------------------|------------|---------------|--------|---------------------|-------|--------|
| PT0    | 0.5            | 0           | 0                 | 553 (±248) | 558 (±161)    | 1.70   | −16.3               | 23    | 82     |
| PT1    | 0.5            | 0.1         | 0                 | 617 (±166) | 641 (±182)    | 1.33   | −13.6               | 23    | 92     |
| PT2    | 0.5            | 0.2         | 0                 | 648 (±269) | 633 (±174)    | 1.39   | −8.40               | 19    | 86     |
| PT3    | 0.5            | 0           | 0.1               | 502 (±128) | 503 (±160)    | 1.27   | −8.50               | 23    | 92     |

If 0.1 mg/mL of CHC was further added and mixed with the solution of pectin (0.5 mg/mL) and TH, the $D_n$ of the TH-loaded pectin/CHC particle (PT1) became 617 nm, and it further increased to 648 nm at a higher feeding concentration of CHC of 0.2 mg/mL (PT2) owing to the additional amount of CHC added into the particles. On the other hand, the particle size of the TH-loaded pectin particles crosslinked by calcium chloride (PT3) was smaller than that of PT1 at the same weight concentrations in the feeds. This is because CHC is a high-molecular-weight polymer that could entangle with pectin as compared to small calcium ions. Still, all the G.S.D. values were smaller than 1.5 for the TH-loaded pectin particles with a crosslinker (PT1, PT2, and PT3). It indicates that the TH-loaded pectin submicron particles with the crosslinker having a narrow particle size distribution can also be synthesized by the continuous-feeding spray-drying system with the ultrasonic atomizer.

The SEM images could provide direct information on the particle size, particle size distribution, and morphology of the TH-loaded pectin particles yet in a dry condition. The sizes of the prepared TH-loaded particles in their wet state (PBS, pH 6.8) were determined by the DLS method at 37 °C. It was found that the initial hydrodynamic diameters (HDs) of the TH-loaded pectin particles in the PBS were from approximately 630 to 712 nm, which were a little larger than those measured by the SEM images in their dry state yet with the same trend in the variation of particle size.

The zeta potential of the TH-loaded pectin particles was approximately −16.3 mV due to the anionic characteristic of pectin as shown in Table 2. It was neutralized by the addition of either the cationic polysaccharide of CHC or the cationic ion of Ca$^{2+}$. It implied that the complex structures of the pectin with the cationic crosslinkers would be formed during the spray-drying process [6,8]. However, the undesired agglomeration phenomena could occur at a higher content of crosslinker in the particles. The spray-dried particles were further analyzed by using ATR-FTIR spectroscopy. As indicated in Figure 5, the spectrum of the pectin sample showed the typical undissociated carboxyl group at 1736 cm$^{-1}$, dissociated carboxyl group at 1609 cm$^{-1}$, and a broad peak at 3362 cm$^{-1}$ denoting the stretching vibrations of the -OH group. For the CHC, the peak at 1626 cm$^{-1}$ was the C=O stretching
vibration of amide I, and 1519 cm$^{-1}$ was the peak for -NH$_3^+$ [25]. Because the spectrum of the sample PC1 containing the pectin and CHC at the weight ratio of 5:1 indicated the change in the peak at 1519 cm$^{-1}$, and the neutralization results observed by the zeta potential tests, it implied that the pectin/CHC complex particles could be formed by the electrostatic interaction between positively charged CHC and negatively charged pectin.

**Figure 4.** SEM images and corresponding particle size distributions of the TH-loaded pectin (a) PT0, pectin/chitosan (b) PT1, (c) PT2, and pectin/calcium ion (d) PT3 submicron particles.
Figure 5. ATR–FTIR spectra of the pectin, CHC, TH particles, and samples PC1 and PT2, in which the numbers indicate the wavenumber of the peaks.

The TH-loaded pectin/CHC submicron particles were further observed using ATR-FTIR spectroscopy. The absorption bands at 1708 and 1670 cm\(^{-1}\) which referred to the carbonyl groups on the TH compound [23], and absorption peaks at 1104 and 1019 cm\(^{-1}\), corresponding to C-O groups of the CHC and pectin, were found in the IR spectrum of the TH-loaded pectin/CHC particles: sample PT2, of which the weight ratio of pectin, CHC and TH were 5:1:1. It denoted that the TH could be loaded successfully in the pectin/CHC
The loading capacity (LC, %) is the amount of drug loaded per unit weight of the TH-loaded particles, and the encapsulation efficiency (EE, %) denotes the percentage of TH that is successfully entrapped into the polymer carriers, which can be determined according to Equations (1) and (2). As shown in Table 2, the TH loading content and efficiency were approximately 19–23% and 82–92%, respectively.

3.3. Release of TH from the Pectin Particles in PBS

For real-time monitoring of the TH released from the pectin/CHC submicron particles, the release profile was determined by measuring the light absorbance of the released medium at the wavelength of 272 nm using a transmission probe immersed in the PBS solution which was coupled to the UV light source. Figure 6 shows the fractional release ($R_{TH}$) profiles of TH from the submicron particles with various compositions at pH 6.8 and 37 °C, in which

$$R_{TH} = \frac{M(t)}{M_\infty}$$

and $M(t)$ and $M_\infty$ are the masses of TH released at time $t$ and the time approaches infinity, respectively.

![Figure 6. TH Fraction released from pectin, pectin/CHC and pectin/calcium ion submicron particles at various times in PBS at pH 6.8 and 37 °C.](image)

For the TH-loaded pectin particles without any crosslinking agent (sample PT0), it was found that at the release time of 30 min, the fractional TH release was 0.61 as indicated in Table 3. With the addition of 0.1 mg/mL CHC solution in the feeding solution, the releasing rate of the TH was retarded for the sample PT1, of which the $R_{TH}$ became 0.44 at 30 min. It was further decreased to 0.36 when the concentration of CHC solution increased to 0.2 mg/mL (PT2). The more the crosslinking structure was formed owing to a higher concentration of CHC, the TH-loaded pectin/CHC complex particles became less flexible. In addition to the cross-linkages formed by the electrostatic interaction between the pectin and CHC, there also existed the possibility of H-bonding among the groups, such as carboxylic acid, hydroxy, methyl ester, amide, amine, carbonyl group, and imidazolium.
groups, within the complex of pectin, CHC and the TH drug. Therefore, the biopolymer chains formed a diffusion barrier, and the diffusion coefficient of TH decreased.

Table 3. Fraction theophylline release (R_{TH}) and kinetic parameters of the Ritger–Peppas model for the theophylline-loaded pectin particles.

| Sample | R_{TH} (30 min) | R_{TH} (180 min) | t_{0.6} (mins) | k     | n     | R^2   |
|--------|-----------------|------------------|----------------|-------|-------|-------|
| PT0    | 0.61            | 0.73             | 28.5           | 0.0615| 0.706 | 0.9804|
| PT1    | 0.44            | 0.71             | 48.5           | 0.0438| 0.681 | 0.9852|
| PT2    | 0.36            | 0.72             | 55.0           | 0.0068| 1.141 | 0.9933|
| PT3    | 0.38            | 0.66             | 66.5           | 0.0304| 0.732 | 0.9887|

The TH-loaded pectin particles could be crosslinked with calcium ions, which resulted from the specific interaction between the calcium ions and galacturonic acid in pectin [26–28]. When a calcium chloride solution of 0.1 mg/mL was added to the precursor solution, sample PT3, the TH release rate became slower than that without the crosslinking agent. After 30 min, the R_{TH} was approximately 0.38, even slower than that from the chitosan-crosslinked pectin particles at the same added amount (PT1). This indicates that the calcium-ion-crosslinked pectin particles were more compact than the chitosan-crosslinked pectin particles, restricting the diffusion of TH. Moreover, Figure 5 shows that the TH release rate gradually decreased to zero after R_{TH} reached approximately 0.6. The release time at R_{TH} = 0.6, denoted as t_{0.6}, became slower by adding either CHC or calcium chloride to the pectin particles.

An exponential equation of the Ritger–Peppas model was proposed to describe the general drug release behavior from the polymeric matrix [29,30].

\[ R_{TH} = kt^n \]  
(4)

where \( k, n \), and \( t \) were the kinetic constant, diffusional exponent, and release time, respectively. Equation (4) is a simplified short-time approximation, and it is valid for the first 60% of the total drug release, that is \( R_{TH} \leq 0.6 \). The model was fitted to the experimental TH release data by using nonlinear least-square regression, and the calculated kinetic parameters are summarized in Table 3. The regression coefficient (R^2) is a statistical measure of how well the regression predictions approximate the real measured data points. For the four TH-loaded submicron particles, all the values of R^2 were greater than 0.98. The results showed good agreement between the model and experimental data. The kinetic constant \( k \) indicated the structural and geometric characteristics of the polymer matrix. It was found as 0.0615 for the TH-loaded pectin particles without any crosslinking agent (sample PT0), and the value became smaller by adding either CHC or calcium ions. The diffusional exponent \( n \) denoted the diffusion mechanism of the drug released from the particles. For non-swellable spherical particles, if the drug release behavior follows the Fickian diffusion, the \( n \) is 0.43. When the exponent \( n \) is greater than 0.43 and less than 1, the transport mechanism is anomalous; that is, it is neither Fickian type nor polymer chain relaxation. For zero-order drug delivery, the exponent \( n \) is one, which implies the drug release rate is independent of time.

For the samples PT0, PT1, and PT3, the values of \( n \) were 0.706, 0.681, and 0.732, respectively, as shown in Table 3. Therefore, the transport mechanism was not pure Fickian diffusion. It was believed that the drug diffusion was affected by the swelling of polymer particles in the PBS. For example, the initial mean hydrodynamic diameter of the sample PT0 measured by the DLS was approximately 630 nm, and it was swollen and became...
915 nm after 30 min. In this study, a volume-swelling ratio (SR) was calculated by the initial hydrodynamic diameter \(DH_0\) and the \(DH\) was measured at 30 min:

\[
SR\% = \frac{DH_{30\text{min}}^3}{DH_0^3} \times 100\% \quad (5)
\]

It was found that the SR decreased with the addition of crosslinking agent. The SRs of the samples PT0, PT1, PT2, and PT3 were approximately 306%, 241%, 221%, and 182%, respectively. Increasing the concentration of crosslinking agent decreased the swelling ratio (PT1 vs. PT2). In addition, the calcium-ion-crosslinked pectin particles exhibited a lower swelling ratio indicating they provided higher crosslinking density than the CHC at the same weight concentration (PT1 vs. PT3). The TH-loaded sample PT2 was prepared from the pectin solution mixed with 0.2 mg/mL of chitosan hydrochloride solution, and the diffusional exponent \(n\) was 1.14. The TH transport mechanism was very close to the zero-order drug delivery, of which \(n = 1\). Because the particles would be swollen during the release test in buffer, the surface area of the TH-loaded particles increased, and the crosslinked polymer matrix became looser. Therefore, the release rate of the TH would increase with time due to the swelling effect. If it could compensate for the decline in the diffusion rate resulting from the decreasing concentration gradient between the particle surfaces and the surrounding medium, it would be possible to keep the TH release at a constant rate.

4. Conclusions

A homemade spray drier coupled with two continuous-feeding streams was constructed. The pectin/chitosan hydrochloride (CHC) particles with diameters of approximately 300 to 800 nm were successfully prepared and tailored by changing the precursor concentration of the fed solution. The possibility of crosslinking between pectin and CHC was inhibited before the spray drying. The theophylline (TH)-loaded pectin particles with a crosslinking agent, such as CHC or calcium chloride, were further fabricated. The Ritger–Peppas model was proposed to describe the TH fractional release from the TH-loaded pectin/CHC submicron particles. For example, for the sample PT2, which was prepared from the mixture of pectin, TH, and CHC solutions of 0.5, 0.2, and 0.2 mg/mL, respectively, the diffusional exponent \(n\) was 1.14, indicating that the TH transport mechanism was very close to the zero-order drug delivery \((n = 1)\). We believe that the structure of the spray-dried TH-loaded pectin/CHC is dependent on the pH of an aqueous solution. It is worth further investigating the influence of pH value on the release of TH.

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References
1. Ahmed, O.; Abdel-Halim, M.; Farid, A.; Elamir, A. Taurine loaded chitosan-pectin nanoparticle shows curative effect against acetic acid-induced colitis in rats. *Chem.-Biol. Int.* 2022, 351, 109715. [CrossRef] [PubMed]
2. Chang, K.L.B.; Lin, J. Swelling behavior and the release of protein from chitosan–pectin composite particles. *Carbohydr. Polym.* 2000, 43, 163–169. [CrossRef]
3. Sun, X.; Cameron, R.G.; Bai, J. Effect of spray-drying temperature on physicochemical, antioxidant and antimicrobial properties of pectin/sodium alginate microencapsulated carvacrol. *Food Hydrocoll.* **2020**, *100*, 105420. [CrossRef]

4. Assif, A.; Lerbert, A.; Uyen, H.T.D.; Neiers, F.; Chambon, O.; Loupiac, C.; Cousin, F. Structural behaviour differences in low methoxy pectin solutions in the presence of divergent cations (Ca$^{2+}$ and Zn$^{2+}$): A process driven by the binding mechanism of the cation with the galacturonic unit. *Soft Matter* **2015**, *11*, 351–360. [CrossRef]

5. Wei, X.; Chen, Z.; Lu, Y.; Xu, H.; Chen, G.; Wu, W. Physicochemical characterization of a pectin/calcium matrix containing a large fraction of calcium chloride: Implications for sigmoidal release characteristics. *J. Appl. Polym. Sci.* **2009**, *113*, 2418–2428. [CrossRef]

6. Maciel, V.B.V.; Yoshida, C.M.P.; Franco, T.T. Chitosan/pectin polyelectrolyte complex as a pH indicator. *Carbohydr. Polym.* **2015**, *132*, 537–545. [CrossRef]

7. Rashidova, S.S.; Milusheva, R.Y.; Semenova, L.N.; Mukhamedjanova, M.Y.; Voropaeva, N.L.; Vasilyeva, S.; Faizieva, R.; Ruban, I.N. Characteristics of interactions in the pectin–chitosan system. *Chromatographia* **2004**, *59*, 779–782. [CrossRef]

8. Bigucci, F.; Luppi, B.; Cerchiarì, T.; Sorrenti, M.; Bettinetti, G.; Rodriguez, L.; Zecchi, V. Chitosan/pectin polyelectrolyte complexes: Selection of suitable preparative conditions for colon-specific delivery of vancomycin. *Eur. J. Pharm. Sci.* **2008**, *35*, 435–441. [CrossRef]

9. Berger, J.; Reist, M.; Mayer, J.M.; Felt, O.; Gurny, R. Structure and interactions in chitosan hydrogels formed by complexation or aggregation for biomedical applications. *Eur. J. Pharm. Biopharm.* **2015**, *94**, 171–181. [CrossRef] [PubMed]

10. Mesehal, M.M.; Gabr, K.E. Effect of interpolymer complex formation of chitosan with pectin or acacia on the release behavior of chlorpromazine HCl. *Int. J. Pharm.* **1993**, *91*, 177–181. [CrossRef]

11. Saladinì, B.; Bigucci, F.; Cerchiarì, T.; Gallucci, M.C.; Luppi, B. Microparticles based on chitosan/pectin polyelectrolyte complexes for nasal delivery of tacrine hydrochloride. *Drug Deliv. Transl. Res.* **2013**, *3*, 33–41. [CrossRef] [PubMed]

12. Herdiana, Y.; Wathoni, N.; Shamsuddin, S.; Muchtaridi, M. Drug release study of the chitosan-based nanoparticles. *Jelisyn* **2022**, *8*, e08674. [CrossRef] [PubMed]

13. Jain, A.K.; Thareja, S. In vitro and in vivo characterization of pharmaceutical nanocarriers used for drug delivery. *Artif. Cells Nanomed. Biotechnol.* **2019**, *47*, 524–539. [CrossRef] [PubMed]

14. Kamaly, N.; Yameen, B.; Wu, J.; Farokhzad, O.C. Degradable controlled-release polymers and polymeric nanoparticles: Mechanisms of controlling drug release. *Chem. Rev.* **2016**, *116*, 2602–2663. [CrossRef]

15. Blanco, E.; Shen, H.; Ferrari, M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nat. Biotechnol.* **2015**, *33*, 941–951. [CrossRef] [PubMed]

16. Gagliardi, M.; Bardi, G.; Gamucci, O.; Mazzolai, B. Targeted drug delivery across biological barriers using polymer nanoparticles. *Future Sci.* **2013**, *96–109.

17. Ziecrińska, A.; Carreiró, F.; Oliveira, A.M.; Neves, A.; Pires, B.; Venkatesh, D.N.; Durazzo, A.; Lucarini, M.; Eder, P.; Silva, A.M.; et al. Polymeric nanoparticles: Production, characterization, toxicology and ecotoxicology. *Molecules* **2020**, *25*, 3731. [CrossRef]

18. Rashki, S.; Asgarpour, K.; TarrahiMofrad, H.; Hashemipour, M.; Ebrahimi, M.S.; Fathizadeh, H.; Khoshidi, A.; Khan, H.; Marzhoseeiny, Z.; Salavati-Niasari, M.; et al. Chitosan-based nanoparticles against bacterial infections. *Carbohydr. Polym.* **2021**, *251*, 117108. [CrossRef]

19. Wu, T.H.; Chou, C.W.; Shen, L.H. Study on the Characterization and controlled drug release carrier of thiolated chitosan-based nanoparticles. *Adv. Mater. Res.* **2012**, *476*, 1480–1483. [CrossRef]

20. Wu, T.H.; Shen, L.H.; Chou, C.W. Study on the Preparation, Property and drug release carrier of chitosan-based nanoparticles for cancer treatment. *Adv. Mater. Res.* **2011**, *284*, 1800–1803. [CrossRef]

21. Sarma, S.; Agarwal, S.; Bhuyan, P.; Hazarika, J.; Ganguly, M. Resveratrol-loaded chitosan–pectin core–shell nanoparticles as novel drug delivery vehicle for sustained release and improved antioxidant activities. *R. Soc. Open Sci.* **2022**, *9*, 210784. [CrossRef] [PubMed]

22. Ismail, A.H.; Al-Bairmani, H.K.; Abbas, Z.S.; Rheima, A.M. Nanoscale synthesis of metal(II) theophylline complexes and assessment of their biological activity. *Nanomaterials* **2020**, *10*, 139–147. [CrossRef]

23. Bobrov, R.; Seton, L.; Dempster, N. The reluctant polymorph: Investigation into the effect of self-association on the solvent-mediated phase transformation and nucleation of theophylline. *Cryst. Eng. Comm.* **2015**, *17*, 5237–5251. [CrossRef]

24. Wei, Y.; Huang, Y.H.; Cheng, K.C.; Song, Y.L. Investigations of the influences of processing conditions on the properties of spray dried chitosan-tripolyphosphate particles loaded with theophylline. *Sci. Rep.* **2020**, *10*, 1155. [CrossRef]

25. Ge, J.; Yue, P.; Chi, J.; Liang, J.; Gao, X. Formation and stability of anthocyanins-loaded nanocomplexes prepared with chitosan hydrochloride and carboxymethyl chitosan. *Food Hydrocoll.* **2018**, *74*, 23–31. [CrossRef]

26. Zhang, W.; Cao, J.; Jiang, W. Effect of different cation in situ cross-linking on the properties of pectin/thymol active film. *Carbohydr. Polym.* **2020**, *128*, 107594. [CrossRef]

27. Braccini, I.; Pérez, S. Molecular basis of Ca$^{2+}$-induced gelation in alginites and pectins: The egg-box model revisited. *Biomacromolecules* **2001**, *2*, 1089–1096. [CrossRef]

28. Fang, Y.; Al-Assaf, S.; Phillips, G.O.; Nishinari, K.; Funami, T.; Williams, P.A. Binding behavior of calcium to polyuronates: Comparison of pectin with alginate. *Carbohydr. Polym.* **2008**, *72*, 334–341. [CrossRef]

29. Serra, L.; Doménech, J.; Peppas, N.A. Drug transport mechanisms and release kinetics from molecularly designed poly(acrylic acid-g-ethylene glycol) hydrogels. *Biomaterials* **2006**, *27*, 5440–5451. [CrossRef]
30. Ritger, P.L.; Peppas, N.A. A simple equation for description of solute release I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *J. Control. Release* **1987**, *5*, 23–36. [CrossRef]

31. Ozmen, M.M.; Dinu, M.V.; Okay, O. Preparation of macroporous poly(acrylamide) hydrogels in DMSO/water mixture at subzero temperatures. *Polym. Bull.* **2008**, *60*, 169–180. [CrossRef]

32. Oh, K.S.; Oh, J.S.; Choi, H.S.; Bae, Y.C. Effect of cross-linking density on swelling behavior of NIPA gel particles. *Macromolecules* **1998**, *31*, 7328–7335. [CrossRef]