# Preparation and Characteristics of High-Amylose Corn Starch/Pectin Blend Microparticles: A Technical Note

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## INTRODUCTION

Delivery of bioactive molecules to specific sites of the digestive system is an important criterion in drug therapies for colonic diseases, such as ulcerative colitis, Crohn's diseases, colon carcinoma, oral administration of proteins, and delivery of vitamins and sensitive food ingredients. Various enteric coatings were developed to protect sensitive compounds from dissolution and decomposition in the gastrointestinal tract. Commonly used enteric coating materials are natural, semisynthetic, and synthetic polymers. These include zein and shellac, amylose acetate phthalate and cellulose derivatives (cellulose acetate phthalate and hydroxyl propyl methyl cellulose phthalate), and various ethylacrylate and methylmethacrylate.[1-4] Most of these materials react to pH changes, and the release of the bioactive molecules is determined by the local pH in the intestine. Specifically, a dramatic increase in the solubility of these polymers occurs at pH starting at 4.8 and up to 7.2. Because the pH in the small intestine is about 6.1 to 8.0, systems based on these materials will release the active compounds in the small intestine and will not reach the colon.[5] Therefore, while protecting the biologically active materials from the acidic environment of the stomach, commonly used polymers do not protect the active ingredients from dissolution and enzymatic digestion in the small intestine. Thus, to reach the colon, the drug delivery systems should be based on polymeric materials that are insoluble in both acidic and neutral environments and not digestible by pancreatic enzymes. A potential alternative to commonly used coatings is ingested starch that escapes digestion in the small intestine and reaches the large bowel. This fraction was given the name resistant starch (RS).[6] Although not digested in the small intestine, RS may be fermented and disintegrated by the microflora in the large bowl. RS-rich fractions can be obtained by hydrothermal treatments and retrogradation of native high-amylose corn starch (HACS).[7] RS is made of short oligosaccharides, and it is very likely that drug delivery systems based on non-cross-linked HACS enriched by RS will need additional physical support. One potential component for this purpose is pectin.

Pectins are nonstarch linear polysaccharides that consist of α-1,4-galacturonic acid and 1,2 D-rhamnose with D-galactose and D-arabinose side chains having average molecular weights between 50,000 and 150,000. Pectin, a structural plant polysaccharide, remains an aggregate of macromolecules in acid environments. At neutral-solution pH, pectin aggregates tend to dissociate and expand and are digested by a large number of microflora of the colon.[8,9] To overcome the problem of high dissolution of pectin in the upper gastrointestinal tract, pectin has been combined with other polymers (polyeletrolyte complexation [eg, with chitosan] or blending with insoluble polymer [eg, ethyl cellulose]). In addition, pectin-based, colon-specific drug delivery vehicles have been developed using a chemically modified pectin polymer.[9-14] Oral controlled drug delivery systems based on blend polysaccharidic matrix are gaining widespread acceptance in the pharmaceutical industries because of their flexibility to obtain a desirable drug-release profile, cost-effectiveness, and broad regulatory acceptance. The composites take the advantages of their parent polymers and/or create useful new properties. Such a blend matrix can be applied for the release of both hydrophilic and hydrophobic drugs and charged solutes.[14]

A cross-linking method has been applied to HACS and extensively studied for the controlled drug release applications.[15-17] Preparation of cross-linked HACS microparticles by the methods other than spray drying involves a tedious process and is unsuitable for large-scale production in the pharmaceutical industry. The process involving simple preparative procedures is preferred for the preparation of sustained-release carriers in the pharmaceutical industries. The spray-drying microencapsulation technique is widely used in the pharmaceutical industries because of its numerous advantages over other microencapsulation

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methods. The advantage of the spray-drying technique for application to microencapsulation is that it is reproducible, rapid, and easy to scale up. Therefore, this article describes the preparation of a new blend (gelatinized HACS/pectin) of microparticles by the spray-drying technique and their characteristics (size, surface morphology, and in vitro drug-release profile). Diclofenac sodium is an ideal drug for incorporation in a controlled-release device to diminish its adverse effects after oral administration and was used as a model drug candidate.

## MATERIALS AND METHODS

### *Materials*

Diclofenac sodium (99.6%) was obtained as gift sample from Cipla Ltd (Mumbai, India). HACS (HYLON VII) was also obtained as a gift sample from National Starch and Chemical Co (Bridgewater, NJ). High-methoxy pectin was purchased from Sigma Aldrich (Steinheim, Germany). All of the other chemicals were of analytical grade and were used without additional purification. Ultrapure water (Billerica, MA) was used throughout.

### *Methods*

#### *Preparation of HACS/Pectin-Blend Microparticles*

The blend polymeric solutions were prepared from various combinations of HACS and pectin solutions. Pectin solutions (2% w/v) were prepared by overnight vigorous mixing of pectin in an aqueous medium. HACS solutions were prepared by thermal treatment. Briefly, aqueous dispersion of 2% w/v HACS was gelatinized at 120°C for 120 minutes and cooled to ambient temperature on a stirring plate. The blend solutions were prepared by mixing HACS and pectin solutions at ratios of 1:1, 1:3, 1:5, 5:1, and 3:1 (HACS: pectin). Diclofenac sodium (0.25% w/v) was dissolved in blend polymeric solution by stirring the mixture for 20 minutes. Then, the drug-loaded HACS/pectin microparticles were obtained by spray drying the polymeric-drug solutions. Spray drying was performed using a SD-04 spray drier (Lab Plant, North Yorkshire, UK), with a standard 0.5-mm nozzle. Spray-drying conditions, such as inlet temperature, liquid flow rate, and compressed-spray airflow were set at 145°C, 2 mL/min, and 1.2 $m^3$/min, respectively.

#### *Measurement of Particle Size*

Particle size was analyzed by dispersing the microparticles in an aqueous solution of Tween 80 (0.1%) using a particle size analyzer (Malvern Mastersizer, Malvern Instruments, Worcestershire, UK).

#### *Loading Efficiency*

About 15 mg of drug-loaded HACS/pectin-blend microparticles were dissolved in phosphate buffer (pH 7.4) by sonication. The resulting solution was passed through a 0.22-μm membrane filter (Millipore), and then the drug content was assayed by measuring the absorbance at 276 nm using an ultraviolet spectrophotometer (Shimadzu 1601PC, Kyoto, Japan). Experiments were performed in triplicate (n = 3), and loading efficiencies were calculated using Equation 1.

$$\text{Loading efficiency}\,(\%) = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100 \qquad (1)$$

#### *Zeta Potential*

Microparticles concentrations of 0.3% w/v were made by dispersing microparticles in KCl solution (pH 7.0). The ζ potential of the microparticles was recorded using laser Doppler anemometry (Malvern Zetasizer, Malvern). Each sample was measured in triplicate.

#### *Surface Morphology*

The surface morphology of drug-loaded HACS/pectin-blend microparticles was examined by means of a Hitachi (Tokyo, Japan) scanning electron microscope. The microparticles were fixed previously on a brass stub using double-sided adhesive tape and then were made electrically conductive by coating, in a vacuum, with a thin layer of platinum (approximately 3 to 5 nm) for 100 seconds at 30 W.

#### *Radiograph Diffraction*

Radiograph powder diffraction patterns of pure diclofenac sodium, placebo HACS/pectin-blend microparticles, and diclofenac sodium-loaded HACS/pectin-blend microparticles were obtained at room temperature using a Philips X' Pert MPD diffractometer (Philips, Eindhoven, The Netherlands), with Co as an anode material and graphite monochromator, operated at a voltage of 40 kV.

#### *In Vitro Drug Release*

The in vitro release of diclofenac sodium from HACS/pectin-blend microparticles was determined using a US Pharmacopeia dissolution apparatus (TW-SM, Wooju Scientific Co, Seoul, South Korea). To suspend the microparticles in the dissolution medium, about 200 mg of microparticles were taken in cellulose dialysis bag

(previously soaked in dissolution medium for 3 hours) containing 3 mL of dissolution medium and tied to the paddle. The in vitro release studies of diclofenac sodium were conducted at a paddle rotation of 100 rpm in 900 mL of phosphate buffer (pH 7.4 and 37°C). An aliquot of the release medium (5 mL) was withdrawn through a sampling syringe attached with 0.2-μm filter at predetermined time intervals (0.5, 1, 2, 3, 4, 5, and 6 hours), and an equivalent volume of fresh dissolution medium, which was prewarmed at 37°C was replaced. Collected samples were then analyzed for diclofenac sodium content by measuring the absorbance at 276 nm using an ultraviolet spectrophotometer (Shimadzu 1601PC). In vitro drug release studies were also conducted separately in 0.1 N HCl solution (pH 1.2) for 2 hours in an identical manner as described above. In vitro release studies were performed in triplicate (n = 3) in an identical manner.

### *Data Analysis*

Values are expressed as mean ± SD. Mean and SD of the results from at least three independent experiments were calculated using Microsoft Excel (Redmond, WA) software.

## RESULTS AND DISCUSSION

### *Properties of Microparticles*

The spray-drying conditions were initially optimized to obtain the product with maximum yield. The optimized conditions were then adopted for the preparation of drug-loaded microparticles. The characteristics of the microparticles prepared in the present study are presented in Table 1. The mean particle size of the microparticles prepared in the present study was in the range of 5.8 to 7.3 μm. The percentage yield of the microparticles was between 72.6% and 80.2%. The encapsulation efficiency of the blend microparticles was impressive. For instance, encapsulation efficiencies of the new blend (HACS/pectin) microparticles were comparatively higher than the plain HACS or pectin microparticles. The encapsulation efficiency of these prepared microparticles was mainly between 80.1% and 94.7%. The surface charge of these microparticles was determined by measuring the ζ potential of these microparticles at a neutral pH. It was found that these microparticles were positively charged. The ζ potential of the microparticles prepared in the present study ranged between 20.3 and 30.8 mV.

### *Surface Morphology*

The surface morphology of new polymeric blend microparticles loaded with the drug was examined by using a scanning electron microscope (see Figure 1). Irregular-shaped microparticles with porous characteristics were obtained with plain pectin or HACS polymeric solution. When pectin was blended with HACS, the microparticles with a uniform spherical shape and a smooth surface could be obtained. However, the ratio between these polymers (HACS-to-pectin) influenced the surface morphology of the microparticles. For instance, the microparticles based on a 1:1 ratio of HACS to pectin exhibited a uniform spherical shape and surface smoothness compared with the other blend ratios. As the concentration of pectin increased in the blend compositions, irregular-shaped microparticles (porous microparticles) could be produced. This can be clearly observed from Figures 1B and 1C. In the case of microparticles based on HACS to pectin ratios of 5:1 and 3:1, the microparticles exhibited more uniform spherical shapes than the 1:3 and 1:5 ratios. This indicates that in the blending of HACS with pectin at appropriate ratios, the uniformly shaped microparticles with smooth surfaces could be prepared by a spray-drying technique.

### *Physical State of the Drug*

X-ray diffraction analyses of the spray-dried HACS/pectin-blend microparticles were performed to characterize the physical state of the loaded drug in the blend polymeric matrix. The characteristic X-ray diffraction spectra of pure drug (diclofenac sodium), placebo HACS/pectin-blend

**Table 1.** The Percentage Yield, Mean Particle Size, Encapsulation Efficiency, and ζ Potential of the HACS/Pectin Blend Microparticles

| HACS-to-Pectin Ratio | Yield (%) | Mean Particle Size (μm) | Encapsulation Efficiency (%) | Zeta potential (mV) |
|---|---|---|---|---|
| Pectin alone | 77.9 | 6.0 ± 1.8 | 80.1 ± 1.1 | 22.1 ± 3.1 |
| HACS alone | 72.6 | 6.3 ± 1.1 | 83.4 ± 2.3 | 20.3 ± 2.3 |
| 1:1 | 78.3 | 6.6 ± 2.1 | 93.5 ± 1.3 | 26.5 ± 3.5 |
| 1:3 | 79.5 | 5.8 ± 1.4 | 89.3 ± 2.5 | 29.2 ± 1.6 |
| 1:5 | 77.4 | 7.3 ± 2.1 | 92.2 ± 3.7 | 25.1 ± 1.8 |
| 5:1 | 79.0 | 7.1 ± 1.8 | 94.7 ± 4.1 | 30.8 ± 2.7 |
| 3:1 | 80.2 | 6.9 ± 1.6 | 93.8 ± 1.6 | 28.2 ± 1.4 |

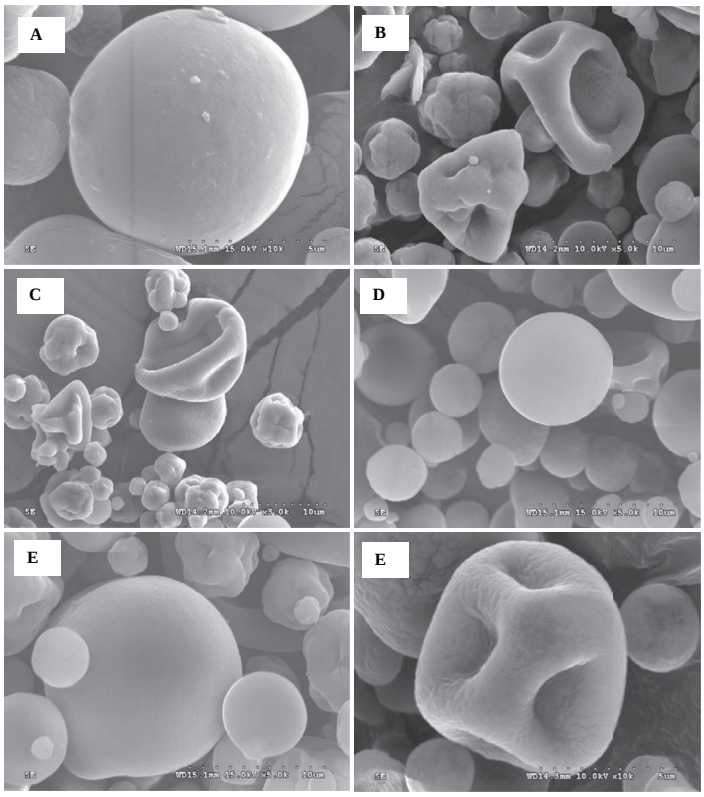


**Figure 1.** Scanning electron microscopy pictures of HACS/pectin blend microparticles based on HACS/pectin 1:1 (A), 1:3 (B), 1:5 (C), 5:1 (D), and 3:1 (E) ratio along with plain HACS microparticles.

microparticles (control), and drug-loaded HACS/pectin-blend microparticles are presented in Figure 2. Characteristic crystalline peaks of diclofenac sodium were observed at 2θ of 6.6°, 8.5°, 15.1°, 19.8°, 20.0°, 24.0°, and 24.9° (Figure 2A), indicating the presence of crystalline diclofenac sodium. Under the present experimental conditions, spray-dried placebo HACS/pectin blend microparticles did not show any peaks (Figure 2B). The characteristic crystalline peaks of diclofenac sodium disappeared after encapsulation in HACS/pectin-blend polymeric matrix (Figure 2C), but instead, only a placebo microparticle pattern was obtained. This indicates that diclofenac sodium is dispersed at the molecular level in the blend polymeric matrix and, hence, no crystals were found in the drug-loaded microparticles.

### *In Vitro Drug Release*

The potential use of spray-dried HACS/pectin microparticles as colon-targeted drug delivery carriers was examined by performing the dissolution studies in gastric (pH 1.2 for 2 hours) and intestinal (pH 7.4 for 6 hours) conditions using diclofenac sodium as a model drug candidate. The plot of cumulative drug release versus time in simulated gastric (pH 1.2) and intestinal (pH 7.4) conditions is shown in Figures 3A and 3B, respectively. The release rates of the drug from spray-dried pectin-plain microparticles were faster than their composite microparticles both in simulated gastric and intestinal conditions. Spray-dried plain pectin microparticles exhibited a higher cumulative drug release in a simulated gastric condition than the plain HACS and all of the HACS/pectin-blend microparticles. Blending of HACS, which is insoluble in gastric fluid (pH 1.2) and neutral environments, with pectin decreased the release rate of the drug from pectin microparticles in a simulated gastric condition. However, the ratio between the HACS and pectin influenced the drug-release profile. With increasing content of the HACS in blend compositions, the release rate of the drug from the pectin microparticles could be retarded in the gastric environment.

In the case of drug-release profiles in simulated intestinal fluid (pH 7.4), the release rate of the drug is similarly higher in plain-pectin microparticles than the HACS/pectin-blend microparticles. The release rate of the drug from plain-pectin microparticles was much faster than any other microparticle formulations. This is very likely attributable to the higher solubility of the pectin at this pH because of the ionization of its carboxylic groups at higher pH values.[9] In addition, previous studies have shown that an addition of another polymer is required to sustain the drug release from pectin-based microparticles.[12-14] In this study, the blending of HACS with pectin resulted in a better-sustained drug-release profile both in gastric and intestinal

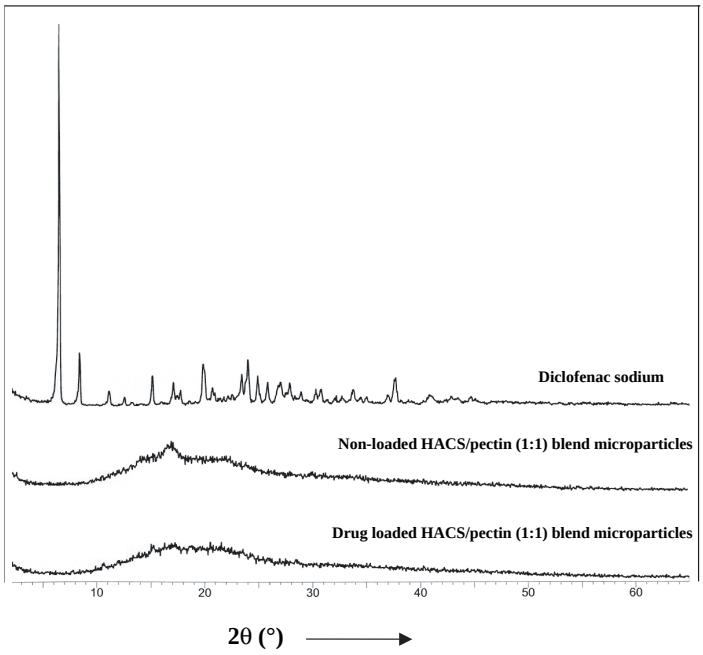


**Figure 2.** Radiograph diffractograms of diclofenac sodium, nonloaded HACS/pectin (1:1) blend microparticles, and drug-loaded HACS/pectin (1:1) blend microparticles.

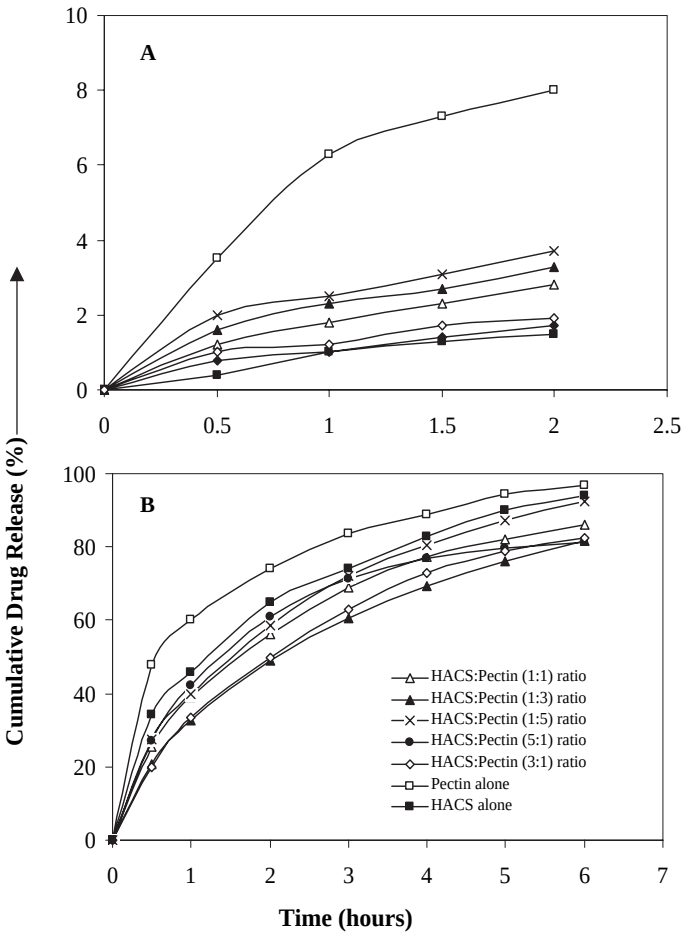


**Figure 3.** Cumulative drug release profiles of plain HACS, plain pectin, and HACS/pectin-blend microparticles in simulated gastric, that is, pH 1.2 (A) and intestina, that is, pH 7.4 (B) conditions.

(pH 1.2 and 7.4) conditions. However, the influence of blend ratios of HACS and pectin on the release rate of the drug from their composite microparticles in simulated intestinal fluid was somewhat different from that observed in the case of the simulated gastric condition. For instance, the release rate of the drug from microparticles based on HACS/pectin 1:3 and 3:1 ratio (HACS to pectin) was slower than the other microparticulate systems. The release profile of the blend microparticles based on a 1:1 ratio (HACS to pectin) was between the release profiles of the microparticles based on 1:5 and 3:1 (HACS to pectin) ratios. HACS-to-pectin (5:1 ratio) blend microparticles exhibited a rapid initial drug release followed by a sustained release profile over the period of 6 hours.

Fishman et al[18] showed that as the HACS content increases in the HACS/pectin-based films, the dissolution of the HACS/pectin-blend films decreases in the intestinal conditions (pH 7.4). In contrast, results of the drug-release study in the current work demonstrated that the dissolution of microparticles might have increased with increasing content of HACS and, hence, the drug release rate from such blend microparticles in the intestinal conditions. Spray-dried polymeric microparticles exhibit different release profiles than those prepared by other methods. Spray drying of polymers results in the modulation of their swelling and dissolution behavior and, hence, the drug release rate in the gastrointestinal fluids. For instance, the spray-dried chitosan microparticles are unsuitable for sustained drug release because of their greater swelling ability and dissolution.[19] In the present study, it was anticipated that the release rate of the drug would be retarded for a longer period of time with increasing content of gelatinized HACS in pectin-based microparticles in the intestinal conditions. But, spray drying of HACS might have resulted in a higher swelling capacity and a dissolution in the intestinal condition (pH 7.4), which may be responsible for a higher drug-release rate from plain HACS and HACS/pectin (5:1 and 3:1) blend microparticles when compared with microparticles based on the 1:3 ratio. This can be clearly observed from the Figure 3. For instance, plain HACS microparticles exhibited a higher cumulative amount of drug release than microparticles based on 5:1 and 3:1 (HACS to pectin) ratios. However, factors such as surface morphology (porous or nonporous [dense]), drug content, interaction of polymers, and physical state of the drug might have also contributed to the unusual drug release behavior from these blend microparticles.

### *Kinetic Models*

To investigate the mode of drug release from HACS/pectin blend microparticles, the release data were analyzed with the following mathematical models: zero-order kinetic (Equation 2), first-order kinetic (Eequation 3), square root of time equation (Higuchi equation, Equation 4), and Korsmeyer equation (Equation 5).

$$Q = k_0 t \tag{2}$$

$$\ln(100 - Q) = \ln Q_0 - k_1 t \tag{3}$$

$$Q = k_{\mathrm{H}} t^{1/2} \tag{4}$$

$$\frac{M_t}{M_\infty} = k t^n \tag{5}$$

In the equations, $Q$ is the percent of drug released at time $t$ and $k_0$, $k_1$ and $k_{\mathrm{H}}$ are the coefficients of the equations, $M_t/M\infty$ is the fraction of drug release at time $t$, $k$ is the release rate constant, and $n$ is the release exponent indicative of the mechanism of release. When $n$ approximates to 0.5, a Fickian/diffusion-controlled release is implied, where $0.5 < n < 1.0$ non-Fickian transport and $n$ is 1 for

**Table 2.** Kinetic Parameters of Drug Release From Plain Pectin, Plain HACS, and HACS/Pectin Blend Microparticles

| | Zero-Order Model | | First-Order Model | | Higuchi Model | | Korsmeyer Model | | |
|---|---|---|---|---|---|---|---|---|---|
| **HACS-to-Pectin Ratio** | $K_o^1$ | $r^2$ | $k_1$ | $r^2$ | $k_H$ | $r^2$ | n | k | $r^2$ |
| Pectin alone | 51.7 | 0.9138 | 1.85 | 0.9909 | 31.42 | 0.9782 | 0.28 | 1.78 | 0.9936 |
| HACS alone | 36.8 | 0.9353 | 1.93 | 0.9933 | 12.13 | 0.9882 | 0.40 | 1.67 | 0.9902 |
| 1:1 | 29.2 | 0.9202 | 1.91 | 0.9942 | 3.91 | 0.9817 | 0.45 | 1.60 | 0.9857 |
| 1:3 | 22.5 | 0.9506 | 1.95 | 0.9990 | 2.48 | 0.9948 | 0.51 | 1.52 | 0.9944 |
| 1:5 | 29.8 | 0.9385 | 1.96 | 0.9961 | 2.77 | 0.9899 | 0.47 | 1.62 | 0.9902 |
| 5:1 | 34.0 | 0.8452 | 1.85 | 0.9377 | 10.95 | 0.9377 | 0.37 | 1.65 | 0.9506 |
| 3:1 | 22.7 | 0.9350 | 1.95 | 0.9947 | 3.34 | 0.9881 | 0.51 | 1.54 | 0.9901 |

zero order (case II transport). When the value of *n* approaches 1.0, phenomenologically one may conclude that the release is approaching zero order.

Dissolution data were analyzed based on Equations 2 to 5, and their results are presented in Table 2. The results showed that the ratio between HACS and pectin had a significant influence on the mechanism of drug release from their blend microparticles in the intestinal condition (pH 7.4). For instance, the release mechanism of drug from microparticles based on 1:1, 1:3, 1:5, and 3:1 (HACS to pectin) blend ratios was found to be by diffusion, because the value of *n* approaches to 0.5 (0.45 to 0.51) and exhibits good correlation ($r^2$ = 0.9857 to 0.999). Whereas in the case of microparticles based on pectin alone, HACS alone, and 5:1 (HACS to pectin) blend ratio, the release mechanism was somewhat complex and might involve both the erosion and swelling controlled diffusion, because the value of *n* lies between 0.28 and 0.40. Poor correlation was observed with the zero-order model.

## SUMMARY AND CONCLUSIONS

The HACS/pectin blend microparticles were prepared by spray-drying technique to obtain effective targeted drug release to the colon. The mean particle size of the microparticles (plain and blend) that were prepared in the present study was between 5.8 and 7.3 μm. The microparticles were positively charged (ζ potential was in the range of 20.3 to 30.8), and the encapsulation efficiency was between 80.1% and 94.7%. The blending of HACS with pectin improved the encapsulation efficiency and decreased the drug dissolution in the gastric condition (pH 1.2) from the pectin-based microparticles. Results of the drug release study indicated that the colonic-controlled drug delivery could be obtained from spray-dried HACS/pectin blend microparticles, and the drug release mechanism was found to be by diffusion or erosion or a combination of both.

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