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Properties of Tableted High-Amylose Corn Starch–Pectin Blend Microparticles Intended for Controlled Delivery of Diclofenac Sodium

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ABSTRACT: This study reports the properties of tableted microparticles based on high-amylose corn starch (HACS)–pectin blend polymers as the controlled release system for diclofenac sodium (DS). HACS–pectin blend microparticles are prepared through a modified process by the spray drying technique, which is a widely used microencapsulation technique in the pharmaceutical industry. The mean particle size of various formulations of blend microparticles is in the range of 5.8–7.3 μm . Fourier transform infrared (FTIR) spectroscopy study reveals the absence of well-defined interaction between HACS–pectin and polymers–DS. The blend microparticles thus prepared were compressed into tablets using the directly compressible excipients. A cross-sectional view of the tablet reveals the presence of nearly spherical shaped particles in the tablet, suggesting that the system chosen is ideal for tableting. *In vitro* drug release study indicates that tableted microparticulate system is found to be suitable for the manipulation of release behavior for DS in the gastrointestinal tract. Release mechanism of the DS from tableted microparticles is by Fickian diffusion since the value of n approaches 0.5.

KEY WORDS: microparticles, controlled release, diclofenac sodium, tableted microparticles, spray drying, pectin, high-amylose corn starch.

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INTRODUCTION

Biodegradable microparticles have been extensively investigated as delivery systems for drugs. In particular, polysaccharide-based microparticles have gained much more attention in developing controlled release microparticulate systems because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance [1,2]. Controlled-release characteristics of microparticles reduce the need for frequent administrations and enhance patient compliance by maintaining *in vivo* drug levels in the therapeutic range [3–6]. Thus, oral controlled release multiple-unit drug delivery systems, such as microparticles, beads, and pellets have gained widespread importance due to their numerous advantages over conventional single-unit dosage forms. Once the tablet or capsule containing multiple units disintegrate, particles spread uniformly throughout the gastrointestinal tract (GIT). This will avoid the release of the drug at one particular site, thus avoiding the risk of toxicity caused by the locally restrained tablet within the GIT. A uniform distribution of multiple units in GIT results in more reproducible absorption and will reduce the risk of local irritations, compared to single-unit systems [7]. Multiple units can be filled into hard gelatin capsules or they can be compressed into tablets. However, the formulation of multiple units into tablets has the advantage of preventing tampering, as in the case of capsules, but the merger of these multiple systems during compression can produce variations in the controlled release of the drug.

Diclofenac sodium (DS) is a nonsteroidal drug having a potent anti-inflammatory, analgesic, and antipyretic effect. It is an inhibitor of prostaglandin synthetase. It is used for the relief of pain and inflammation in conditions, such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout, and those following some surgical procedures. It has an unpleasant taste and causes gastric irritation. DS is mainly absorbed from the GIT [8]. It is a phenylacetic acid derivative with a pKa value of 4.0. It is practically insoluble in acidic solutions but dissolves in intestinal fluid and water. It is generally known that DS gets into the blood within 30 min and reaches the maximum blood concentration (C_{\max}) within 1.5–2.5 h following oral administration of an enteric coated tablet. The maximum average concentration in the blood is between 0.7 and 1.5 mg L⁻¹ [9]. The oral bioavailability is around 60% with an excretion half-life between 1.1 and 1.8 h [9]. Controlled release multiple-unit oral dosage forms are effective in achieving optimal therapy with drugs that have a narrow therapeutic range of blood concentration or that eliminate rapidly and reduce the risk of gastric

irritation at one particular site because of the uniform distribution of the drug throughout the GIT.

Polymeric microparticles are widely studied carriers for the controlled release application of drugs. Encapsulation of drugs into polymeric matrix can be achieved by techniques, such as emulsion, coacervation, spray drying, [10] etc. Among the several microencapsulation methods, spray drying technique is widely used in the pharmaceutical industries because it involves one-stage continuous process, yields reproducible results and can be applied for large-scale production [3–6]. Tableting of polymeric microparticles would result in controlled release of the drug. After tableting of microparticles, the particles may remain intact within the tablet without undergoing merging or rupturing and, hence, drug release will take place from the individual microparticles; if not, the microparticles may merge or rupture to become bigger compacts. In such cases, the release will occur from compacts in the tablet formulation. Ideally, the drug release should occur from the individual particles, which should not be affected by the compression process. However, excipients used in tableting should provide a sufficient cushioning effect to withstand the compression force and, thereby, prevent the merging or rupturing of the microparticles.

In continuation of our ongoing program of research on the development of polysaccharide micro- and nanoparticulates for the controlled delivery of bioactive molecules [3–6,11,12], this article reports the properties of tableted high-amylose corn starch (HACS)–pectin blend microparticles as a novel oral controlled delivery system for DS. In this regard, a previous article [6] describes the encapsulation of DS in HACS–pectin blend microparticles and their properties (size, encapsulation efficiency, surface morphology, and drug release behavior). This article mainly focuses on the tableting of DS-loaded HACS–pectin blend microparticles thus prepared and the characteristics of tableted microparticles. The polymers employed in the present study were HACS and pectin because both are polysaccharides, and microparticle-based blend matrix exhibits a more effective controlled release manner than that based on a single polymer.

MATERIALS AND METHODS

Materials

Diclofenac sodium (99.6%) was obtained as a gift sample from Cipla Ltd, Mumbai, India. HACS (HYLON[®] VII) was also obtained as a gift sample from National Starch and Chemical Company, New Jersey, USA.

High-methoxy pectin was purchased from Sigma Aldrich (Germany). Microcrystalline cellulose, lactose, poly(vinylpyrrolidone) K-30, and magnesium stearate were purchased from Duksan Chemicals, Korea. All other chemicals were of analytical grade and used without further purification. Ultrapure water (Millipore, USA) 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 vigorous mixing of pectin overnight 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 min, and cooled to ambient temperature on a stirring plate. The gelatinized HACS solution was blended with pectin under high speed (5000 rpm, 20 min) homogenization using a Young Ji HMZ 20DN stirrer (Hana Instruments). Blend solutions were prepared at ratios of 1 : 1, 1 : 3, 1 : 5, 5 : 1, and 3 : 1 (HACS: Pectin). DS (0.25%w/v) was dissolved in blend polymeric solution by stirring the mixture for 20 min. 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, 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 m³/min, respectively.

Measurement of Particle Size

The 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, UK).

FTIR Spectroscopy

After tableting the microparticles, the HACS–pectin and blend (HACS and pectin) polymers–DS interaction was studied by Fourier transform infrared (FTIR) spectroscopy. FTIR spectra of DS, HACS, pectin, placebo-tableted HACS–pectin blend microparticles, and drug-loaded tableted HACS–pectin blend microparticles were obtained by using an FTIR spectrometer-430 (Jasco, Japan). The samples (DS or HACS or pectin or placebo-tableted HACS–pectin blend microparticles or drug-loaded tableted HACS–pectin blend microparticles) were previously ground and mixed thoroughly with potassium bromide, an

infrared transparent matrix, at 1:5 (sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders, under a force of 5 ton for 5 min in a hydraulic press. Thirty scans were obtained at a resolution of 4 cm^{-1} , from 4500 to 400 cm^{-1} .

Surface Morphology

The surface morphology of drug-loaded HACS–pectin blend microparticles, tableted HACS–pectin blend microparticles, and fractured part of tableted microparticles were examined by means of a Hitachi (Japan) scanning electron microscope. The powders or tablet or fractured part of tableted microparticles were previously fixed 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/palladium ($\approx 3\text{--}5\text{ nm}$), for 120 s and at 30 W.

Tableting of HACS–Pectin Blend Microparticles

Pure DS and DS-loaded HACS–pectin blend microparticles were tableted using directly compressible microcrystalline cellulose and directly compressible lactose as diluents. Poly (vinylpyrrolidone) K-30 was used as the dry binder, while magnesium stearate was used as the lubricant. Each tablet contained pure DS or DS-loaded HACS–pectin blend microparticles equivalent to 25 mg of DS. Tablets were compressed by using an IR hydraulic pellet maker (Jasco Corporation, Japan) under a pressure of 300 kgf cm^{-2} for 15 s of dwell time, uniaxially. An exactly weighed quantity of the powder mixture was filled into a die of 12.8 mm diameter using little pressure and, then, hydraulic pressure was applied to form the tablet. Tablets were evaluated for their hardness, friability, and disintegration properties. Disintegration tests were performed in 0.1 N HCl (pH 1.2) at 37°C .

Drug Content of Tableted Microparticles

Each tablet was crushed into powder in a mortar and then the powder was soaked in 100 mL of phosphate buffer solution (pH 7.4) for 24 h followed by sonication for 5 min. The solution was passed through a $0.2\text{ }\mu\text{m}$ membrane filter (Millipore, USA) and then the drug content was determined by measuring the absorbance at 276 nm using a UV spectrophotometer (Shimadzu 1601PC, Japan). Experiments were repeated in triplicate in an identical manner.

In vitro Drug Release

Drug release from the pure DS tablet and tableted microparticles was studied by using a dissolution tester (TW-SM, Wooju Scientific, Co.,

Korea) at a stirring speed of 100 rpm. Three tablets from each batch were tested using 900 mL of dissolution medium (phosphate buffer, pH 7.4), maintained at 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 h) and an equivalent amount of fresh dissolution medium, which was prewarmed at 37°C, was replaced. Collected samples were then analyzed for DS content by measuring the absorbance at 276 nm using a UV spectrophotometer (Shimadzu 1601PC, Japan). *In vitro* release studies were performed in triplicates ($n = 3$) in an identical manner.

Data Analysis

Values are expressed as mean \pm standard deviation. Mean and standard deviation of the results from at least three independent experiments were calculated using Microsoft Excel[®] (Redmond, WA, USA) software.

RESULTS AND DISCUSSION

Preparation and Characteristics of Tableted HACS-Pectin Blend Microparticles

The encapsulation method by spray drying is simple and rapid, since spray drying combines drying of feed solution and embedding of the drug into the polymeric network process in a one-step operation [3–6,13]. Among the various biopolymers available for the encapsulation of drugs, polysaccharides display a perfect biocompatibility and biodegradability, which are the basic characteristics for polymers used as biomaterials. In addition, these biomaterials are economical. Therefore, they are widely used in pharmaceutical industries for the preparation of sustained release formulations and, in several cases, they play a fundamental role in determining the release rate from the dosage form [6]. Polysaccharidic biodegradable matrices are of interest since the degradation of natural products like starch occurs naturally in the human body. Pectins are polysaccharides rich in galacturonic acid and galacturonic acid methyl ester units. Pectin is rapidly decomposed by the colon microflora. Hence, pectin-based systems are studied for targeting the drugs to the colon. As an unfavorable factor, pectin undergoes dissolution in the upper GIT (pH 1.2). To overcome the problems of pectin dissolution, pectin is usually combined with ethyl cellulose, Eudragit[®], sodium alginate, and chitosan [1,2]. Controlled

release formulations of cross-linked HACS are thoroughly investigated [14–16]. In this study, an effort is made to prepare noncross-linked HACS controlled release tableted formulation by blending gelatinized HACS with pectin. HACS is insoluble in both acidic and neutral environments and is not digestible by pancreatic enzymes. Therefore, the advantage of blending HACS with pectin is that it decreases the dissolution of pectin in gastric environment, a disadvantage associated with pectin polymer; and more effective colonic delivery of drug or sensitive bioactive molecules can be obtained through the blend systems of HACS and pectin. In other words, the composite (blend systems) systems always take the advantages of their parent polymers and/or create new useful properties [17]. Hence, the present study describes the formulation of HACS–pectin blend microparticles into tablets as a colon-targeted system and their characteristics. The present blend matrix system can be applied for the release of both hydrophilic and hydrophobic drugs and charged solutes to the colon. The blend microparticles were prepared by spray drying method and the microparticles thus prepared were compressed into tablets by using directly compressible excipients. The schematic representation of the preparation process of the tableted HACS–pectin blend microparticles is shown in Figure 1, and the composition of the various formulations is presented in Table 1.

The results of the particle size distribution of microparticles, hardness, thickness, and disintegration time of tableted microparticles are presented in Table 2. The mean particle size of various formulations of tableted microparticles was in the range of 5.8–7.3 μm . The mean particle size was affected by the surface morphology (porous or nonporous) of the microparticles. For instance, microparticles with an irregular shape exhibited a higher mean particle size than the uniform shape particles [6]. The DS-loaded HACS–pectin blend microparticles thus prepared were successfully compressed into tablets. The hardness of various formulations of tableted microparticles was in the range of 4.5–5.5 kg cm^{-2} . The thickness and disintegration time of all the blend microparticulate tablets were between 3.85 and 3.89 min and 17 and 28 min, respectively. The results of the assay of the tableted microparticles indicated uniformity in drug content in the tablets since the drug content was found to vary between 95.4 and 98.3%.

FTIR Spectroscopy

The possible HACS–pectin and drug–polymers interaction was investigated by FTIR spectroscopy. This technique is useful in such a

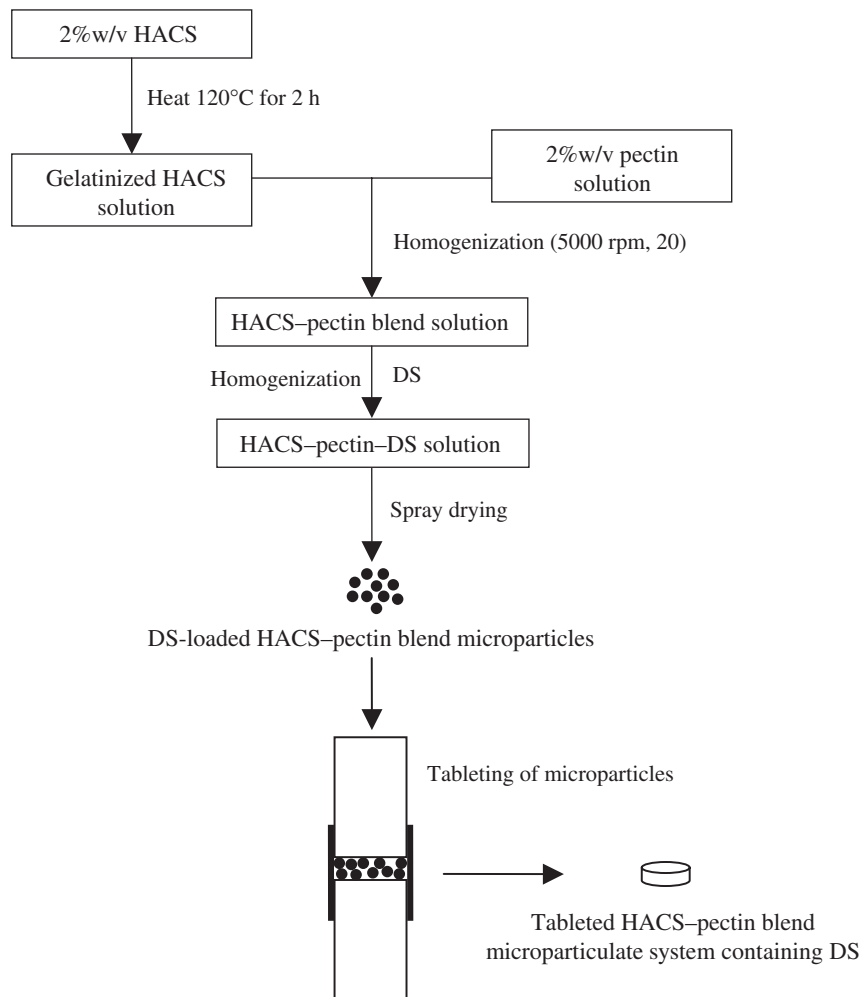


Figure 1. Schematic representation of the preparation process of tableted high-amylose corn starch (HACS)-pectin blend microparticles containing diclofenac sodium (DS).

study since the formation of new groups due to possible interaction can be easily observed by the presence or absence of new functional group peaks in the FTIR spectra. The FTIR spectra of DS, HACS alone, pectin alone, placebo-tableted HACS-pectin blend microparticles, and DS-loaded tableted HACS-pectin blend microparticles are presented in Figure 2. Characteristic peaks of DS are observed at 746, 1305, 1405,

Table 1. Composition of various formulations (in mg).

Tablet content	Formulation code					
	F1	F2	F3	F4	F5	F6
	Drug-loaded HACS–pectin blend microparticles					
	HACS : pectin ratio					Pure drug
	1 : 1	1 : 3	1 : 5	3 : 1	5 : 1	
Drug-loaded HACS–pectin blend microparticles or pure drug	242	265	248	241	238	25
Microcrystalline cellulose	250	250	250	250	250	250
Poly(vinylpyrrolidone) K-30	30	30	30	30	30	30
Lactose	121.5	98.5	115.5	122.5	125.5	338.5
Magnesium stearate	6.5	6.5	6.5	6.5	6.5	6.5
Total weight	650	650	650	650	650	650

Table 2. Properties of tableted HACS–pectin blend microparticles.

Formulation code	Drug content		Microparticles particle-size distribution (%)			Thickness (mm) ^a	Disintegration time (min) ^a
	of tablets (%) ^a	Hardness (kg cm ⁻²) ^a	<i>D</i> ₁₀ (μm)	<i>D</i> ₅₀ (μm)	<i>D</i> ₉₀ (μm)		
F1	95.4 ± 1.4	4.6 ± 0.2	4.1	4.5	5.5	3.85 ± 0.02	18 ± 0.8
F2	97.8 ± 2.1	4.8 ± 0.1	3.8	4.0	4.8	3.89 ± 0.04	20 ± 1.2
F3	96.1 ± 1.8	4.5 ± 0.3	4.7	5.2	6.1	3.87 ± 0.05	17 ± 0.7
F4	98.3 ± 1.3	4.7 ± 0.2	4.4	4.9	5.7	3.85 ± 0.03	19 ± 0.6
F5	95.7 ± 2.2	4.9 ± 0.1	5.1	5.8	6.9	3.86 ± 0.04	21 ± 0.4
F6	96.8 ± 1.7	5.5 ± 0.4	^b	^b	^b	3.81 ± 0.03	28 ± 1.0

^aValues are expressed as mean ± SD, *n* = 3.

^bNot applicable.

1454, 1508, 1556, and 1575 cm⁻¹ (Figure 2(A)), whereas HACS exhibited its characteristic peaks at 526, 574, 937, 1018, 1079, 1155, 1338, 1371, 2927, and 3444 cm⁻¹ (Figure 2(B)). Pectin showed characteristic peaks at 536, 555, 636, 1029, 1076, 1145, 1419, 1635, 2360, 2940, and 3397 cm⁻¹ (Figure 2(C)). After blending of HACS with pectin, the presence and absence of characteristic peaks associated with specific structural characteristics of the individual polymer were noted. The spectra of HACS–pectin blend systems were equivalent to the addition spectrum of HACS and pectin (Figure 2(D)). These results indicate the absence of a well-defined interaction between HACS and pectin.

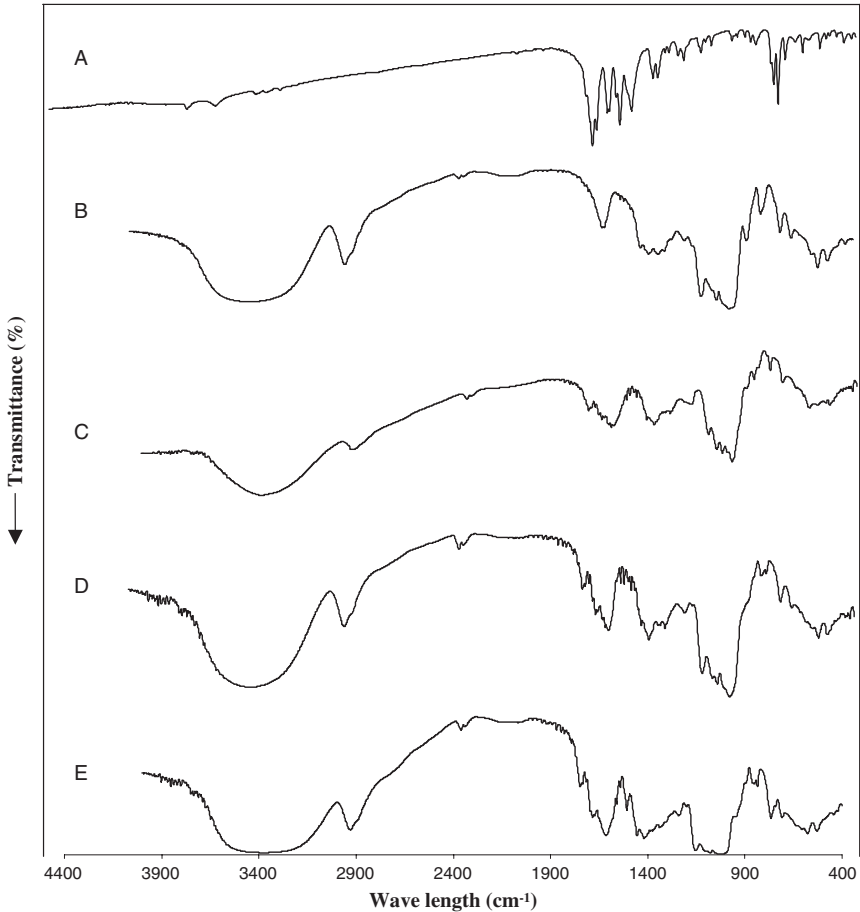


Figure 2. FTIR spectra of DS (A); HACS (B); pectin (C); placebo-tableted HACS-pectin blend microparticles (D); and DS loaded tableted HACS-pectin blend microparticles (E).

After tableting the blend microparticles, the spectra of DS-loaded tableted HACS-pectin blend microparticles is a mixture of characteristic peaks of DS, HACS, and pectin (Figure 2(E)) indicating the absence of interaction between DS and polymers (HACS and pectin).

Surface Morphology

The surface morphology of DS-loaded HACS-pectin blend microparticles and tableted microparticles was observed by SEM. The blend

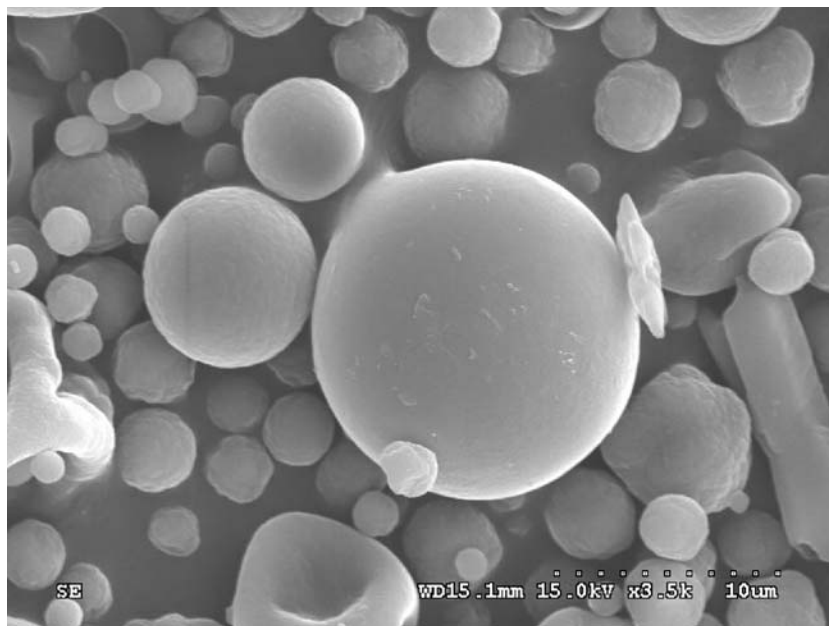


Figure 3. Scanning electron micrograph of HACS–pectin blend microparticles loaded with DS.

microparticles prepared in the present study were a mixture of uniform and nonuniform shape particles. However, in a previous study [6], it was observed that the shape of the blend microparticles was affected by the ratio between HACS and pectin. The increase in the volume ratio of HACS leads to a change of morphological characteristics as the surface of the microparticles becomes porous and the size increases. In all the cases, HACS–pectin blend microparticles exhibited a smooth surface (Figure 3). When compressed, the microparticles were still intact and maintained their shape. A scanning electron micrograph of the cross section of the tableted microparticles is given in Figure 4, from which it can be seen that, within the tablets, microparticles are present as individual particles without compacting during compression. This was further confirmed by taking the micrograph of the surface of the tablet. This view is given in Figure 5. It appears that DS-loaded HACS–pectin blend microparticles are compressed effectively without affecting their shape. Since this is an ideal requirement for producing the tableted microparticles, the procedure used in this research is suitable for tableting.

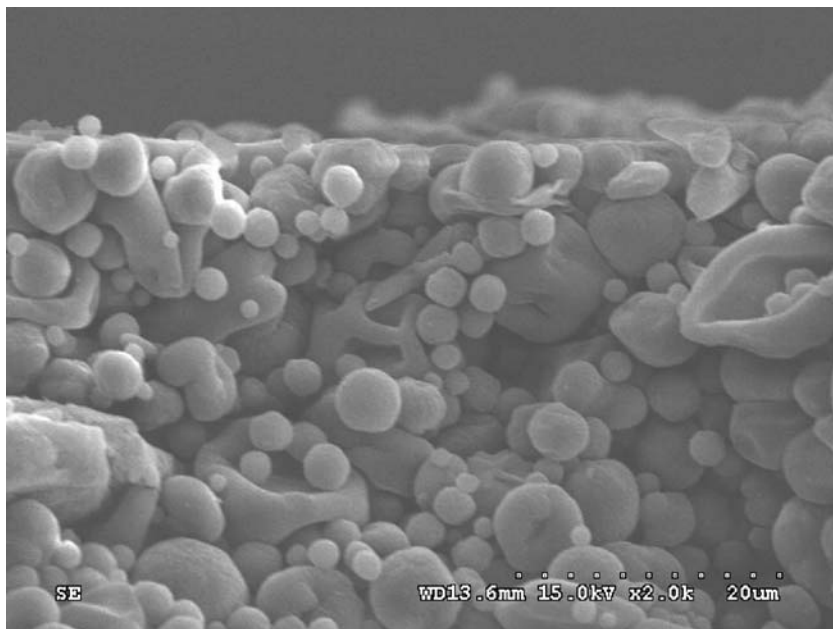


Figure 4. Scanning electron micrograph of the fractured part of the tableted HACS-pectin blend microparticles loaded with DS.

***In vitro* Drug Release**

The release rate of the drug from microparticles based on polysaccharides can be modulated by using cross-linked or modified polymer, or blending of two or more polymers. For instance, modified HACS or pectin has been demonstrated as controlled polymers. Past literature indicates that blending or cross-linking process for pectin is necessary to obtain controlled release of drugs [14–16,18,19]. Therefore, pectin has been combined with other polysaccharides to prevent the dissolution of pectin in the upper part of the GIT and to obtain controlled release of the drug in the lower part of the GIT [2,19,20]. However, cross-linking processes by methods other than the spray drying method involve tedious processes and are unsuitable for large-scale production in the pharmaceutical industries. With the aim of demonstrating a new method for the preparation of controlled release carriers based on HACS and pectin, in the present study, HACS was gelatinized by heat treatment and blended with pectin to modulate the release rate of DS from pectin or HACS-based drug

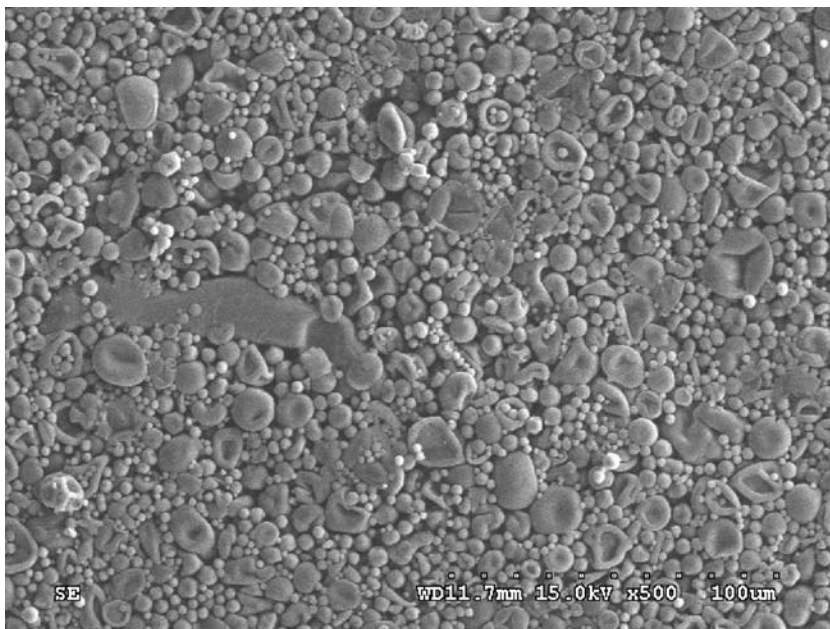


Figure 5. Scanning electron micrograph of the surface of the tableted HACS–pectin blend microparticles loaded with DS.

delivery carriers. The microparticles thus prepared were compressed into tablets. The release rate of the DS from conventional tablets was rapid and more than 95% of the drug was released within 30 min of the dissolution study (see Figure 6). Tableted HACS–pectin blend microparticles exhibited controlled release of the drug. However, the cumulative amount of drug release was affected by the ratio between HACS and pectin. For instance, tableted microparticles based on 1:3 (HACS:pectin) blend ratio exhibited lower cumulative amount of drug release when compared to 1:1, 1:5, 3:1, and 5:1 ratios. More specifically, tableted microparticles based on 1:3 or 3:1 (HACS:pectin) blend ratio were found to be better formulations since they exhibited effective sustained drug release, compared to other formulations. Tableted microparticles based on 5:1 (HACS:pectin) blend ratio exhibited a higher cumulative amount of drug release than any other formulations in the initial period (up to 3 h) followed by a slower release (see Figure 6). It appears that the porous structure of these microparticles could be responsible for the higher cumulative amount of drug release.

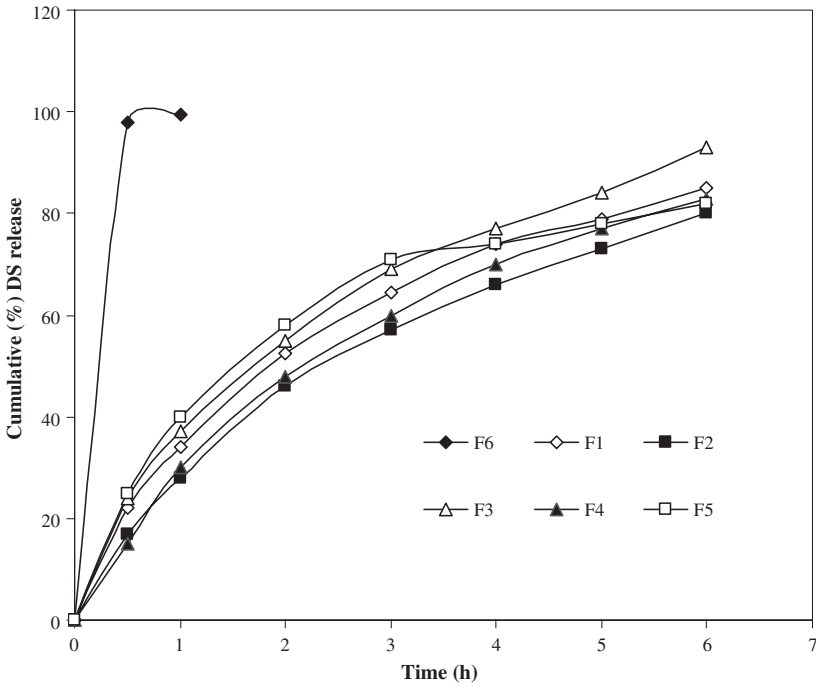


Figure 6. Cumulative amount of DS release (% release) with time from various formulations of tableted HACS–pectin blend microparticles along and tablet containing DS alone (conventional tablet).

The release mechanism of DS from tableted HACS–pectin blend microparticulate systems was analyzed by using the equation [21]:

$$\frac{M_t}{M_\infty} = kt^n$$

where M_t/M_∞ is the fractional release of the drug, t the release time, k is a constant, incorporating structural and geometrical characteristics of the device, and n the diffusional exponent and characterizes the type of release mechanism of the drug during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in the case of Fickian diffusion, $n = 0.50$; for zero-order release (Case II transport), $n = 1$; and for Supercase II transport, $n > 1$. The obtained values of k (kinetic constant), n (diffusional exponent), and r^2 (correlation coefficient) are presented in Table 3. The values of n were estimated by

Table 3. Estimated values of n (diffusional exponent), k (kinetic constant), and r^2 (correlation coefficient) following linear regression of $\log(M_t/M_\infty)$ versus $\log(t)$ for various formulations.^a

Formulation code	n	k	r^2
F1	0.44	1.59	0.9915
F2	0.50	1.51	0.9992
F3	0.46	1.60	0.9935
F4	0.50	1.53	0.9960
F5	0.30	1.68	0.9473

^aValues are obtained using mean cumulative drug release data of three experiments.

linear regression of $\log(M_t/M_\infty)$ versus $\log(t)$, and these values were approaching 0.50, indicating that the release of DS from the tableted microparticles was by Fickian diffusion. Good correlation was obtained with all the formulations except formulation F5, indicating that the release mechanism was somewhat complex since the value of n was 0.30 (see Table 3).

CONCLUSIONS

The spray drying method described here permits one to obtain drug-loaded microparticles constituted by polymeric blends of two polysaccharides, HACS and pectin. The spray-dried microparticles can be easily compressed into tablets and are able to modulate drug release for different durations of time, depending on their composition. In particular, the combination of HACS and pectin at 1:3 and 3:1 (HACS:pectin) ratios leads to more effective controlled drug release. These formulations can be proposed as controlled delivery systems for the oral administration of DS.

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