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CHITIN AND CHITOSAN AS DISINTEGRANTS IN PARACETAMOL TABLETS

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ABSTRACT

Chitin and chitosan as disintegrants in paracetamol tablets were evaluated and compared to four commonly used disintegrants. Tablets containing chitosan showed faster disintegration, greater dissolution and was slightly softer than those containing chitin. An increment in concentration of these polymers caused markedly faster disintegration and better dissolution while an increase in compressional force showed opposite effects. Aging slightly altered the disintegration and dissolution. Tablets containing 7% of chitosan disintegrated within one minute which was much faster than those containing corn starch and microcrystalline cellulose but slightly slower than those containing sodium starch glycolate and croscarmellose sodium. However, their dissolution profiles were non-significantly different from those of the latter ones.

Crystallinity, degree of acetylation, chain length and particle size were attributed to the efficiency of chitin and chitosan. Moisture sorption and water uptake were found to be the major mechanisms of disintegration while dissolution related to the swelling capacity.

INTRODUCTION

Over the years many materials have been proposed as tablet disintegrants and have become commercially available. Starches are the most widely used tablet disintegrants. In addition to starches, a large variety of materials have been used and reported to be effective as tablet disintegrants. Such substances include Veegum HV, agar, bentonite, cellulose product, natural sponge, cation-exchange resin, alginic acid, guar gum and more modern disintegrants such as cyclodextrin polymer, soya polysaccharides, cross-linked casein, etc. [1]. The mechanisms of tablet disintegration have been extensively studied. They are water sorption, swelling, heat of wetting, capillary action, annihilation of cohesion forces between particles in presence of water, followed by particle-particle repulsion. Several mechanisms are perhaps involved in the disintegration process. There is no doubt that the water uptake is the first step in any process of disintegration. The rate of water absorption has been implicated as an important mechanism [2-3].

Two substances from the marine resources may be used as tablet disintegrants. These materials are chitin and chitosan. Chitin, a structural constituent in the shells of crustacean and insect, is an acetylated polyamine, which is biodegradable and non-toxic. It is the most abundant natural polymer, after cellulose. It is a close chemical relative of cellulose, and like cellulose, can be modified both chemically and physically to produce materials with a wide variety of potentially useful properties. It can also be produced in a deacetylated form known as chitosan. A variety of applications of chitin and chitosan have been proposed. Both chitin and chitosan can be produced and cast into tablets, films, gels, beads and so on. Over the years, there have been a number of references to the use of chitin and chitosan derivatives as pharmaceutical excipients in formulation [4-9].

In this study, paracetamol was chosen as a model drug since it was a sparingly water-soluble drug and used in high dose administration, 500 mg per tablet. Therefore the results of tablet disintegrant could be clearly observed. The objectives of this study were to investigate the feasibility of chitin and chitosan as tablet disintegrants, their optimum concentrations and the mechanism by which they functioned as disintegrant. The physicochemical and pharmaceutical properties of these powders and as disintegrant tablets were investigated. Paracetamol tablets containing these polymers were compared to those of other commonly used

disintegrants, corn starch (CS), sodium starch glycolate (SSG), microcrystalline cellulose (MCC) and croscarmellose sodium (CCS). The stability of drug tablets containing disintegrants was also studied.

EXPERIMENTAL

Materials

The following substances were obtained from commercial sources without further treatment; paracetamol (Srichans-United Dispensary, Thailand), chitin(J) and chitosan(J) (Tokyo Kasei, Japan), chitin(U) and chitosan(U) (Unicord, Thailand), CS (Pharmaceutical Sciences Co., Thailand), SSG (Explotab^{R}, Edward Mendell, USA), MCC (Avicel^{R} PH101, Asahi Chemical Industry, Japan), CCS (Ac-di-sol^{R}, FMC, USA).

Methods

1. Evaluation of Chitin and Chitosan Powders.

Chitin and chitosan powders were evaluated for crystallinity by a powder X-ray diffractometer (Joel, JDX 8030, Japan) which used target Cu, voltage 45.0 ku and scanning from 5-40^{o} with 2θ. IR spectra were measured to identify and to determine the degree of acetylation and chain length of the polymer by using an infrared spectrometer (Perkin Elmer, 1760X, USA). The measurement was made by the KBr disc method. The powders were also detected for the degree of acetylation and chain length of polymer by using an electron impacted mass spectrometer (Joel, TMS-DX-300, Japan) equipped with a mass data analysis system (Jeol, JMA 2000, Japan). The amount of protein in powder was determined by Macrokjeldahl method using Kjeltic (KD-0.2). A multiple factor of 6.25 was used for calculation.

The morphology of the different powders was determined by a scanning electron microscope (Joel, JSM-T 220A, Japan) at required magnification and SEM photomicrographs were taken. Particle size distribution of each powder was examined by sieve analysis, using a nest of sieve and an electromagnetic sieving machine (Josef Deckelman, Germany). Sample of ten grams was analyzed and 35 minutes were the shaking time. Weight size was the product of the arithmetic mean size of the openings and the percentage retained on the smaller sieve. The moisture

content of disintegrant was determined by using a pan of moisture determination balance (Ohaus, USA). The weight of moisture loss on drying was read directly.

The swelling capacity of particle was the inverse ratio of the initial sedimentation volume of disintegrant powder in medium and the bulk volume after well dispersion and overnight standing. Deionized water and diluted hydrochloric acid (1:100) were both used as medium.

2. Evaluation of Pure Chitin and Chitosan Tablets

The amount of water uptake was determined on a 500 mg pure disintegrant tablet of 11 mm diameter and compressed on a flat face punch of Carver hydraulic press (Perkin Elmer, USA) at 1500 pounds. The determination was carried out on an apparatus as previously described [10]. The change in the length of liquid column in the capillary tube with time was recorded. The moisture sorption of the disintegrant tablets was determined after stored at 26±1°C in a dessicator of 75% relative humidity. The weight gained by the exposed samples was the weight of the moisture absorbed.

3. Preparation of Paracetamol Tablets.

The composition of paracetamol tablet formulations was presented in TABLE 1. Wet granulation method was performed. The tablets were compressed on an instrumented Stoke single punch tabletting machine (Yiuhang, Thailand) using 1/2 inch flat face punches, with compressional forces of 600 and 900 pounds.

4. Evaluation of Paracetamol Tablets.

The hardness of tablets was determined by using a hardness tester (Schleuniger-2E, Germany), expressed in kilopond unit. The percentage of friability was examined by using a Roche friabilator (Erweka, USA). The tablets were subjected to 100 drops. The disintegration time in seconds was determined by using a USP XXII apparatus (Hanson Research, USA). Deionized water at 37± 1°C was used as immersion medium. The percentage of drug dissolved was determined followed the USP XXII method under the monograph of paracetamol tablet using a dissolution apparatus (Hanson Research, USA).

The amount of water uptake from tablets containing different concentrations of chitin and chitosan was additionally determined.

TABLE 1
The Composition of Paracetamol Tablet Formulations

Ingredient	Amount (mg/tab)
Paracetamol	500
Lactose	5
PVP K30	15
Disintegrant	*
Magnesium stearate	5
* Chitin(J)	1.5, 3, 5, 7% of drug
Chitin(U)	1.5, 3, 5, 7% of drug
Chitosan(J)	1.5, 3, 5, 7% of drug
Chitosan(U)	1.5, 3, 5, 7% of drug
Corn starch	5% of drug
Sodium starch glycolate	5% of drug
Microcrystalline cellulose	10% of drug
Croscarmellose sodium	2% of drug

5. Stability Study

Paracetamol tablets of all formulations were exposed to 45°C and 75% RH for 5 days before evaluation as in 4 except the determination of water uptake.

RESULTS AND DISCUSSION

1. Evaluation of Chitin and Chitosan Powders.

The X-ray diffractograms of chitin and chitosan from both sources are illustrated in FIGURE 1. It could be seen that chitin(U) was in crystalline form since it exhibited some sharp peaks in the X-ray diffractogram while other polymers were in amorphous form because there was no prominent peak.

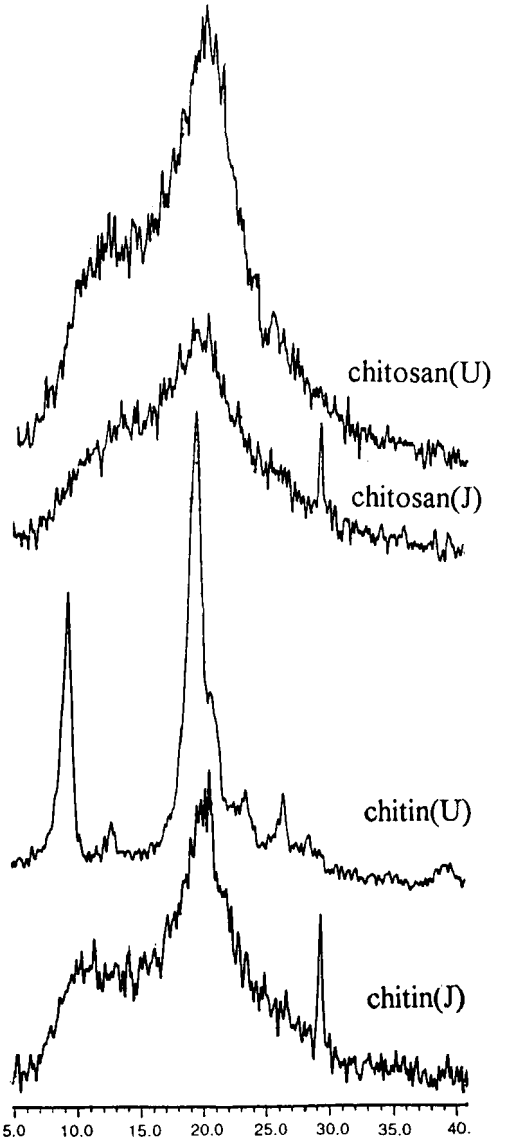

FIGURE 1

Powder X-Ray Diffractograms of Chitin and Chitosan.

All IR spectra in FIGURE 2 were divided into 3 zones, between 3600-3200 cm-1 indicating νOH (free, 3650-3580 cm-1), νOH (bonding, 3550-3200 cm-1), νNH2 (3500-3400 cm-1) and νNH (3520-3400 cm-1); between 1694-1515 cm-1 indicating νC=O (1694-1650 cm-1) and δNH (bending, 1650-1515 cm-1) and between 1170-1114 cm-1 indicating C-O-C stretching. It could be seen that the spectrum of chitin(J) was different from that of chitin(U) but was quite similar to those of chitosan. The chitosan spectrum differed from that of chitin in that the new band at 1590 predominated over the one at 1665 cm-1 and the band at 1550 was absent [11]. Therefore, chitin(J) was likely to be chitosan. However, it could be attributed to the amorphous state of chitin(J) as shown in the X-ray diffractogram. The IR absorption spectra of the same polymer in the crystalline and amorphous states could differ [12]. Some specific intermolecular interaction in crystalline polymer may lead to sharpening or splitting of certain bands, while some conformation in one phase may lead to band characteristic exclusively of either crystalline or amorphous materials. It was also quite difficult to differentiate chitin and chitosan since chitiosan still had νC=O remaining in the molecule. However, it was suggested that higher peak of νC=O when compared to other peak such as peak between 3200-3600 cm-1, indicated higher degree of acetylation [13]. From the IR spectra, it could be stated that the degree of acetylation decreased in the following order: chitin(U) > chitosan(J) > chitin(J) > chitosan(U).

In order to estimate the polymer chain length, the peak intensity of C-O-C between 1170-1114 cm-1, usually 3 peaks, compared to other peak, particularly peak between 3600-3200 cm-1 was conducted. Higher peak ratio indicated longer polymer chain. Unexpectedly, it was found that chitosan had higher peak ratio, therefore longer chain than chitin. Generally, chitosan, a deacetylated chitin, should have shorter chain length since the degree of polymerization of chitin might decrease during the deacetylation process [14].

There were 4 major fragments, as shown in FIGURE 3, m/z 43, 44, 58 and 59 which were $-CO-CH_3$, CO_2, $-NH-CO-CH_3$, and $-CH(OH)-CH-NH_2$, respectively, in the mass spectra generated from chitin and chitosan. Chitin should have all 4 fragments while chitosan of 100% deacetylation should contain no fragment at m/z 43 and 58. The truth that all commercial chitosan might contained acetyl group, therefore, chitin and chitosan could not be differentiated by the ratio intensity of peaks 43 and 58. However, comparison of either peak at m/z 43 or 58

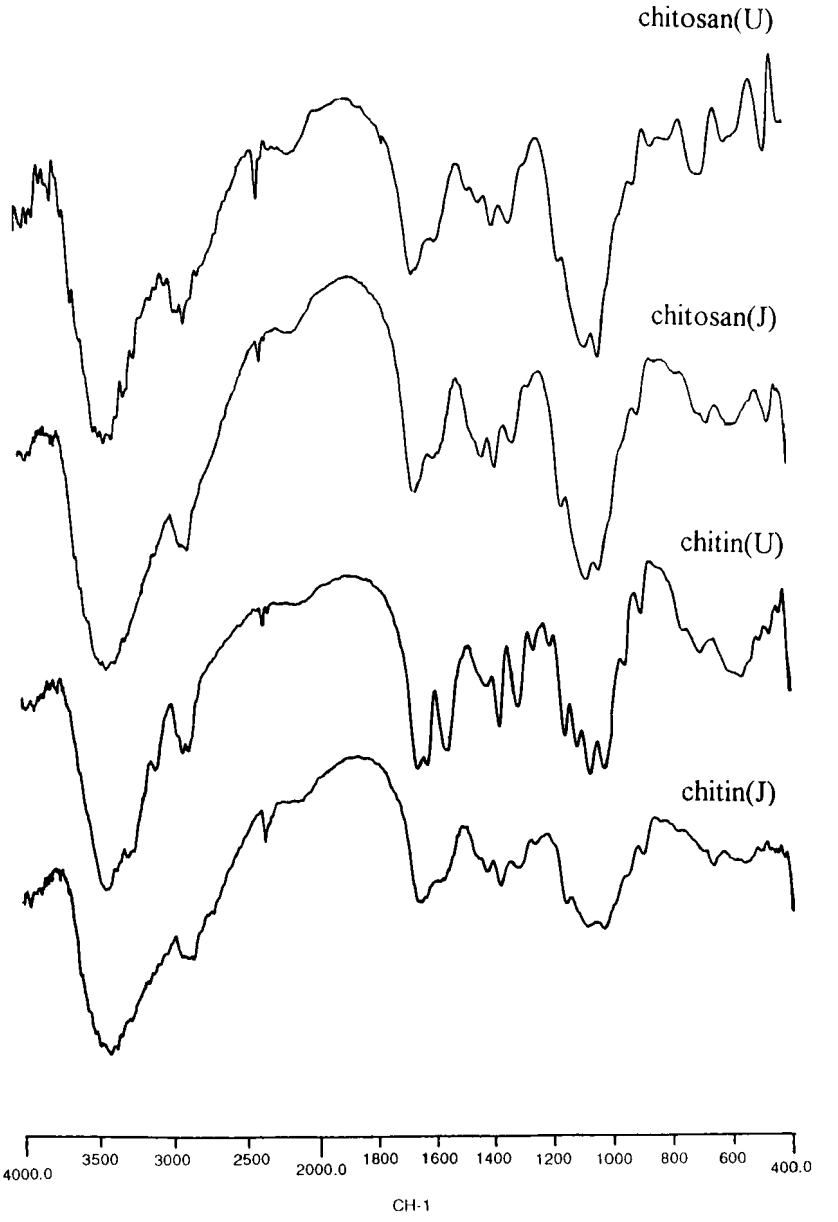

FIGURE 2

IR Spectra of Chitin and Chitosan.

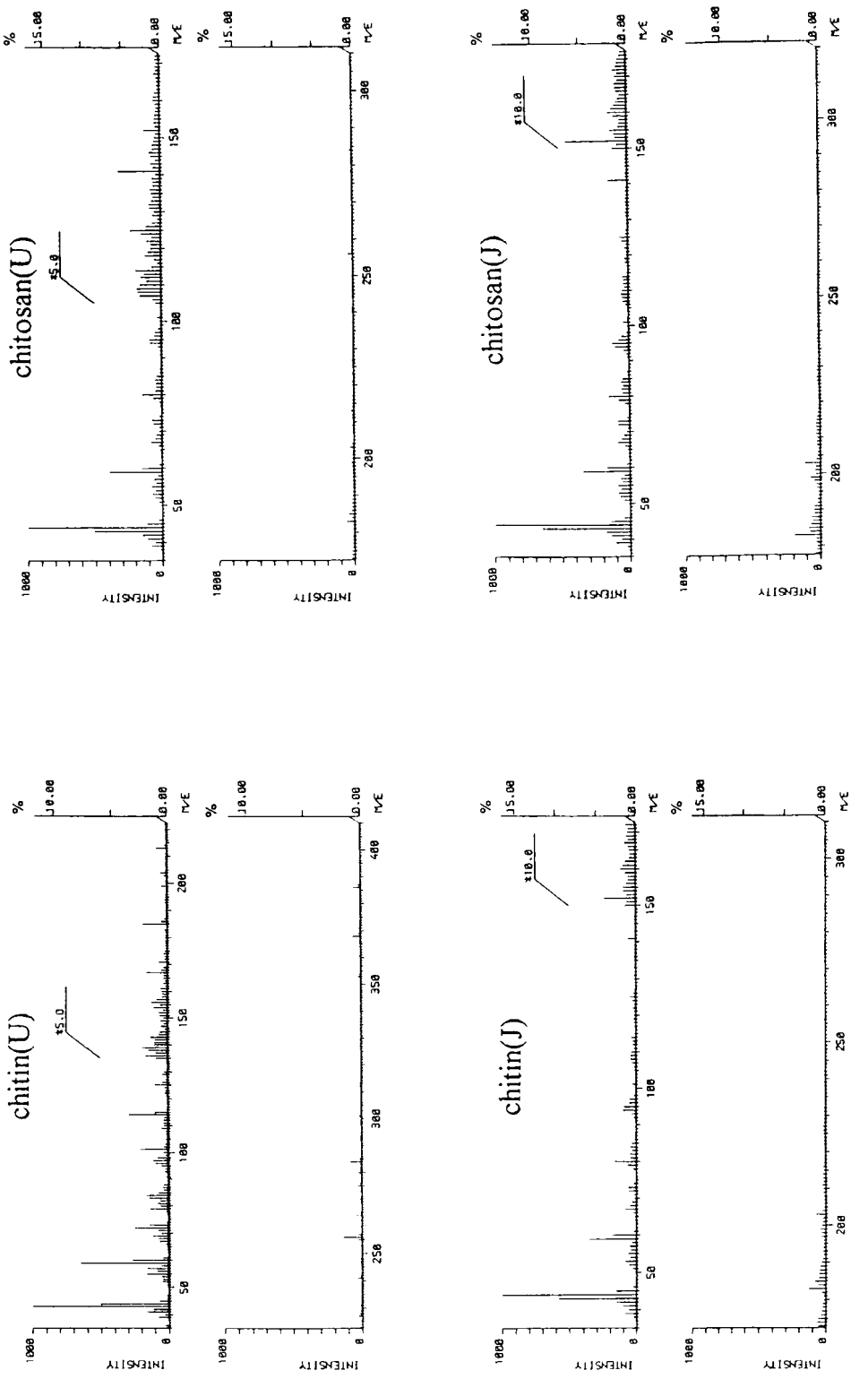

FIGURE 3

Mass Spectra Fragmentation Pattern (EIMS) Generated from Chitin and Chitosan.

of the two spectra was possible, assuming that the same amount of sample was conducted. Higher peak intensity at m/z 43 or 58 indicated higher degree of acetylation. It was apparent that the degree of acetylation was ranked: chitin(U) >> chitosan(J) > chitin(J) > chitosan(U). The result was corresponding to that of IR spectra. It was also evident that chitin(J) was chitosan.

The estimation of chain length of chitin and chitosan may base on the principle that high intensity of fragment at m/z 161 (chitosan 1 unit or monomer) or at m/z 203 (chitin 1 unit or monomer) would display on short chain depolymerization or hydrolysis of short chain polymer. On the contrary, fewer units or monomers of chitin or chitosan indicated long chain depolymerization. According to this principle, mass spectra in the region of m/z 150-300 were focused. Among these four powders, chitin(U) evidently had the shortest chain length since it generated the most abundant and intense peaks at this particular region followed by chitosan(J), chitin(J) and chitosan(U), respectively. However, it was also noted that the result was different from that of IR spectra. Additional analysis such as molecular sieve exclusion chromatography was suggested.

The determination of the percentage of protein content indicated that chitin(J), chitosan(J) and chitosan(U) had quite similar protein content of 40.66, 41.64 and 43.45%, respectively, while chitin(U) had the least amount of 34.28%.

The SEM photomicrographs of chitin and chitosan from different sources are shown in FIGURE 4, respectively. It was apparent that the particles of chitin(J), chitin(U), chitosan(J) and chitosan(U) possessed as irregular, flake-like shape. These polymers were much different in particle size. It could be noticed that chitin(J) powders contained the largest particle size among all polymers. The size then decreased in the following order: chitosan(J), chitosan(U) and chitin(U), respectively. The particle size distribution by sieve analysis is illustrated in FIGURE 5. The result indicated that most particles of chitin(J) and chitosan of both sources had larger size of ≥ 250 μm whereas the size of chitin(U) was 180-250 μm. In addition, powder of chitin(U) had a wider range of size distribution than those of other polymers.

The moisture content of these polymers, presented as percentage of loss on drying, decreased in the following order: chitin(J), 8.96% > chitosan(U), 5.70% > chitin(U), 4.36% > chitosan(J), 2.33%.

The swelling capacity of disintegrant powders in deionized water and diluted hydrochloric acid is shown in FIGURE 6. In deionized water, all samples

were swollen and settled to opaque sediment layer but the volume of the swollen samples marginally varied. Swelling capacity of pure disintegrant powders in deionized water could be ranked as followed: chitosan(J) > chitosan(U) > chitin(J) ≥ chitin(U). The absence of the hydrogen bonding between the sheets of sugar ring of chitin and chitosan explained the ease that these polymers could be swollen in water to produce hydration [15]. The difference in degree of hydration possibly depended on crystallinity, chain length, protein content and degree of acetylation. In addition, the molecular structure of chitin was more rigid than chitosan, causing less swollen in the former one [14]. The capacity of swelling in diluted hydrochloric acid of these polymers was markedly different from that in water except chitin(U). Chitin(J) and chitosan of both sources tremendously increased their swelling capacity and a dramatic change occurred. These three polymers changed to a voluminous translucent mass which was highly gelatinous. Chitosan dissolved in diluted hydrochloric acid solution and only chemically treated or acid hydrolyzed chitin, formed viscous solution, whereas chitin swelled but insoluble in diluted acid [8]. The translucent mass of chitosan(J) seemed to be less viscous than that of chitosan(U). This could be explained that the chain length of chitosan(J) was shorter than chitosan(U) as previously suggested in the result of mass spectra. Chitin(J) in diluted acid, though gelatinous, still had a jelly opaque sedimentation layer. This could possibly be that chitin(J) was more likely to be chitosan or had degree of acetylation less than chitin(U) as indicated in IR and mass spectra, or hydrolysis occurred when it was in diluted HCl, thus formed viscous solution. The swelling capacity of chitin(J) in acid was significantly different and greater than chitin(U).

2. *Evaluation of Pure Polymer Tablets*

The amount of water uptake of chitin and chitosan tablets at compressional force of 1500 pounds is shown in FIGURE 7. It was evident that the amount of water uptake decreased in the following order: chitin(J), chitosan(J), chitosan(U), and chitin(U), respectively. The rate of water uptake of disintegrants then gradually decreased against time. There were different possible explanations for the difference of water uptake between chitin and chitosan such as difference in crystallinity [16]. Amorphous materials undoubtedly absorbed more water. Since protein residues remained with chitin even after the most drastic alkali treatment, difference in the protein content of the material, especially chitin or chitosan might

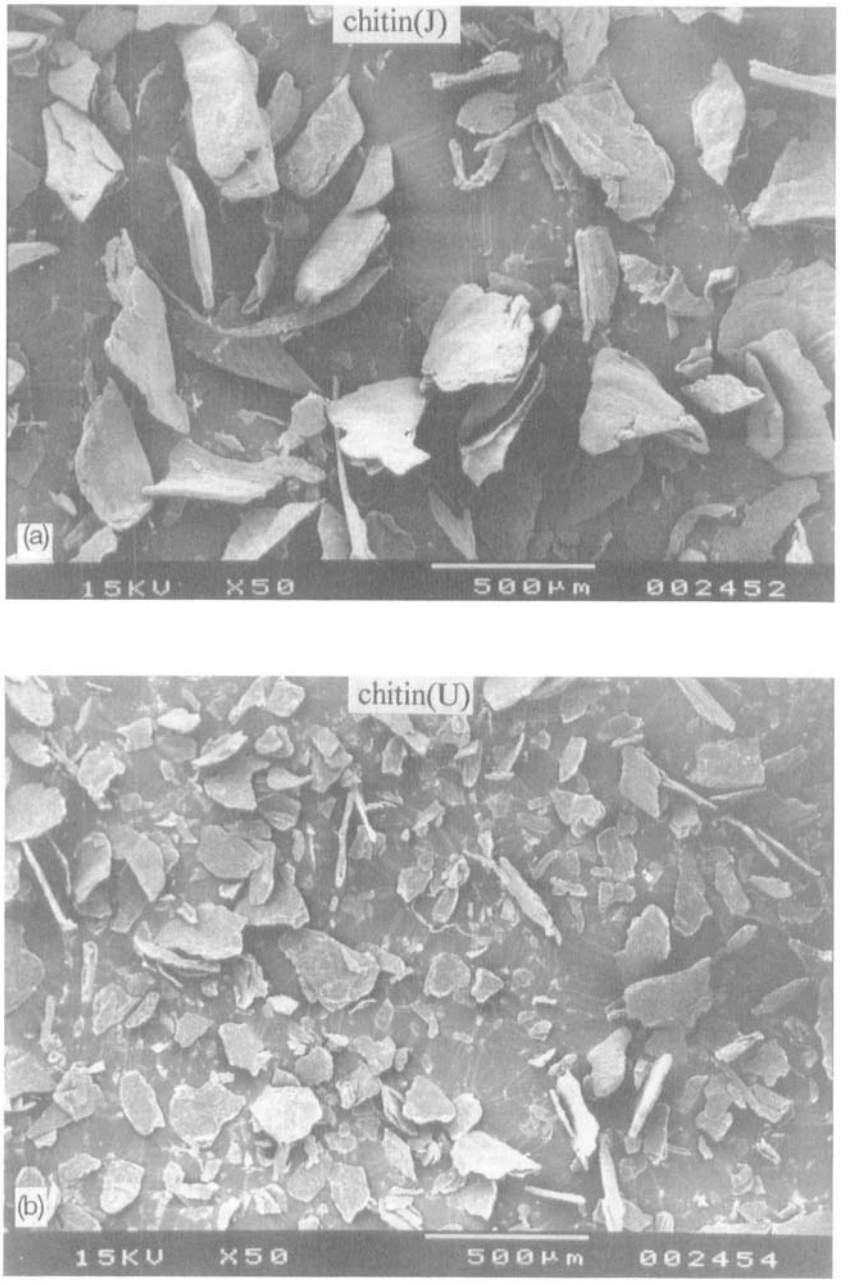

FIGURE 4

SEM Photomicrographs of Chitin and Chitosan Powders.

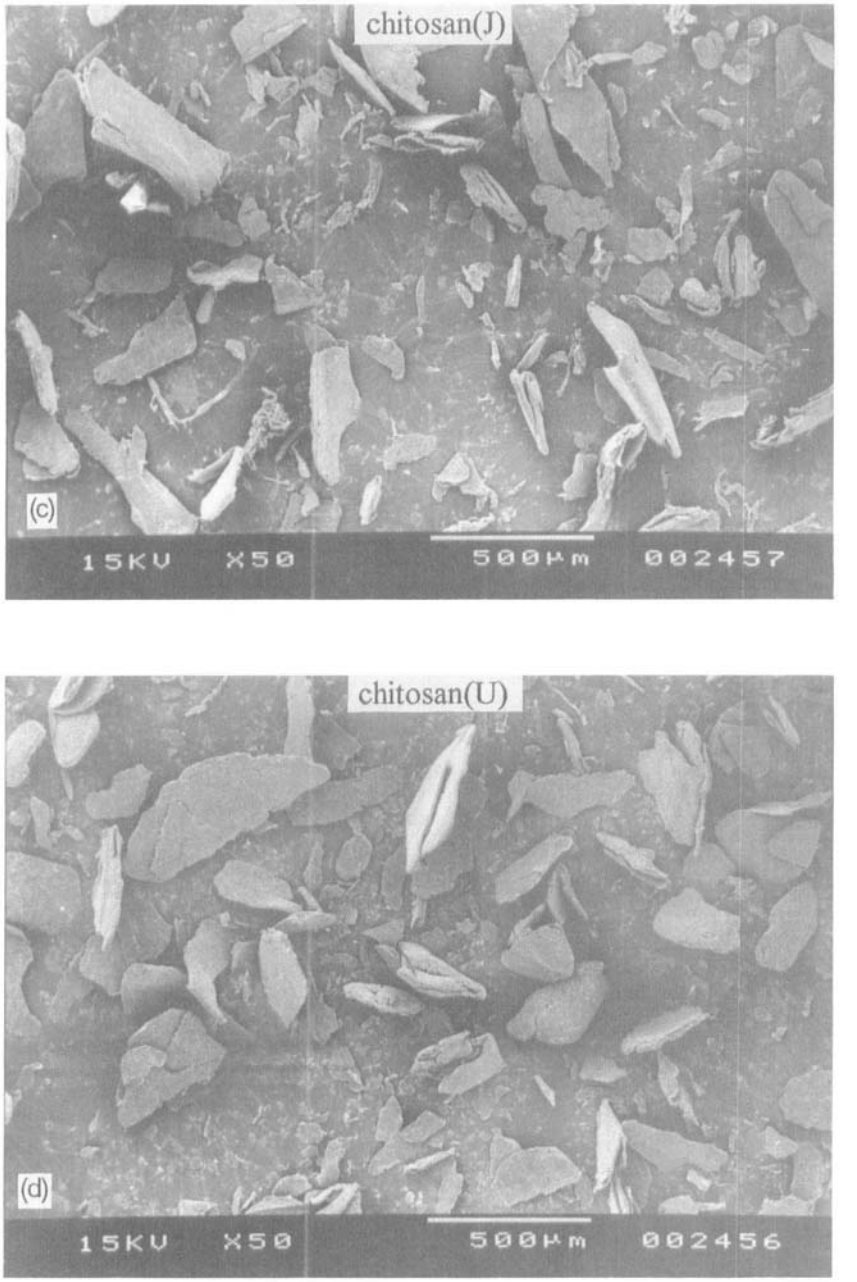

FIGURE 4. Continued

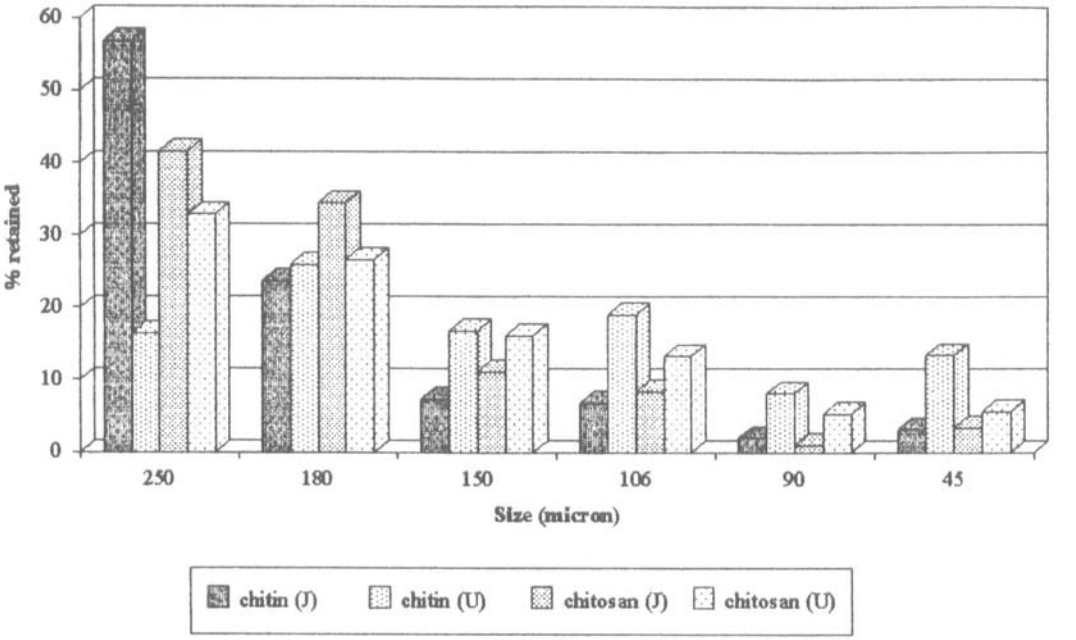

FIGURE 5
Histogram for the Particle Size Distribution of Chitin and Chitosan Powders.

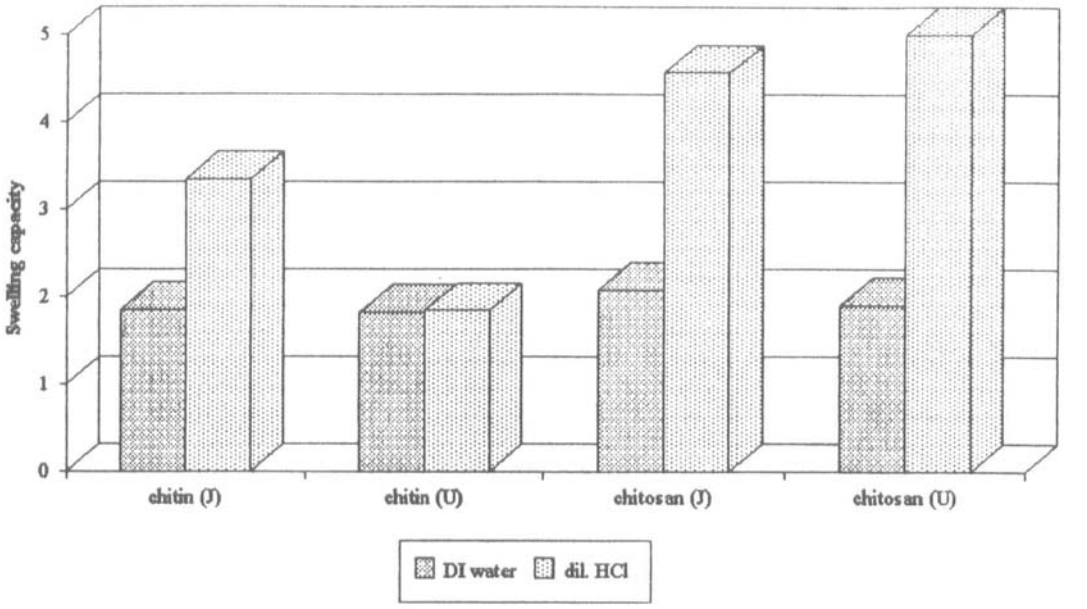

FIGURE 6
Swelling Capacity of Chitin and Chitosan Powders in Deionized Water and Diluted Hydrochloric Acid

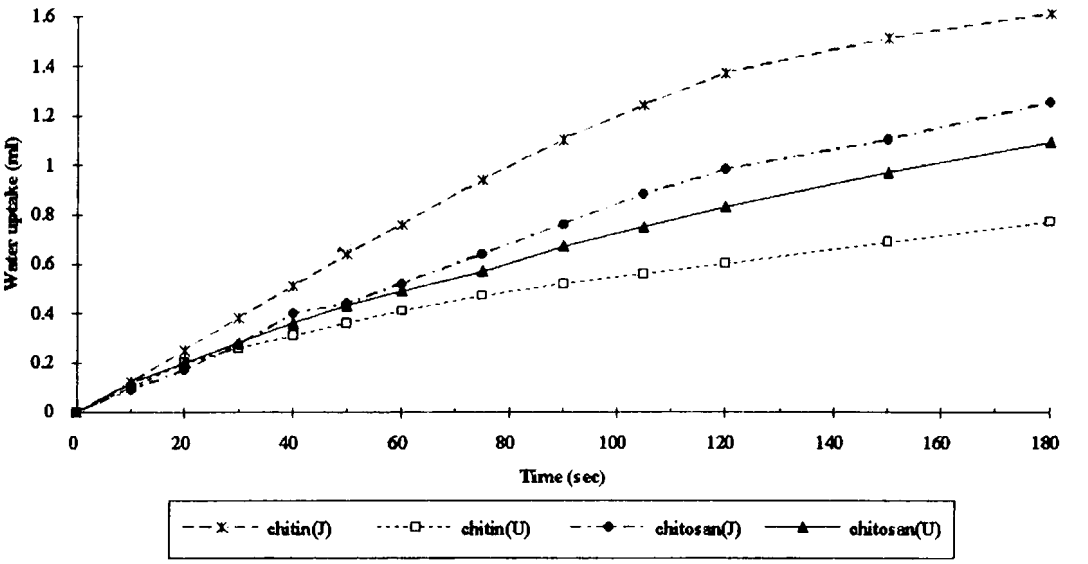

FIGURE 7
Water Uptake Profiles of Chitin and Chitosan Tablets.

also affect the water uptake properties [13]. However, it could not conclude from this investigation that the protein content of these polymers related to their water uptake. It was also noticed that water uptake related to the particle size. Larger particle exhibited substantially greater extent of water uptake than did smaller particles.

The percentage of moisture sorption of different polymer tablets after exposure to 75% relative humidity at room temperature against time was plotted and illustrated in FIGURE 8. The data indicated that after 48 hours, chitosan(J) exhibited the highest moisture sorption, followed by chitin(J), chitosan(U), and chitin(U), respectively. However, chitin(J) was ranked the third after chitosan(J) and chitosan(U) at the first 4 hours.

3. Evaluation of Paracetamol Tablets

The mean values of hardness of all batches of tablets were between 7.5 to 8 and 9.2 to 10 kiloponds at the compressional forces of 600 and 900 pounds, respectively, as shown in TABLE 2. It was found that tablet hardness was not

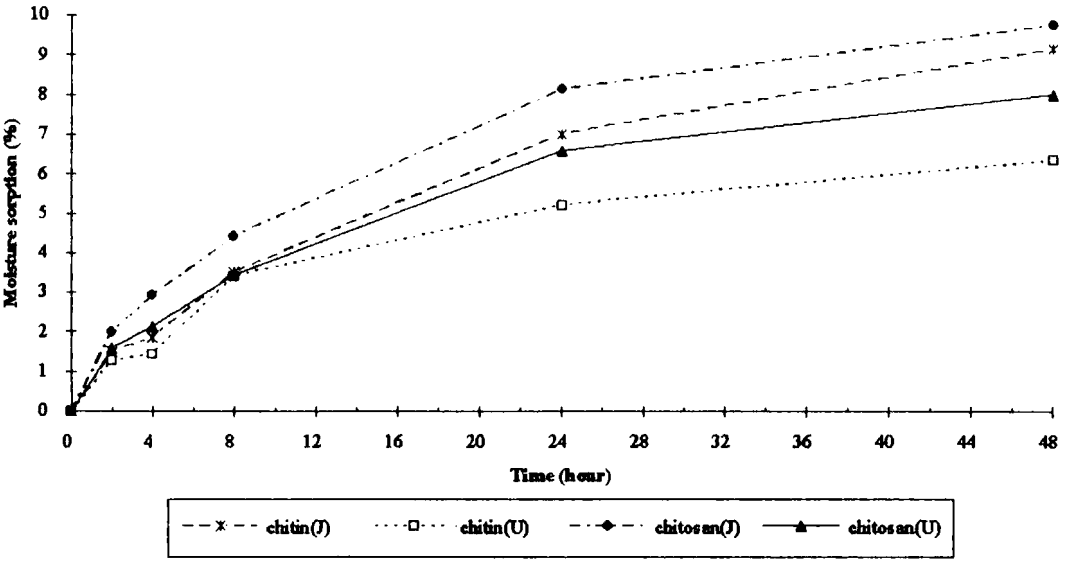

FIGURE 8
Moisture Sorption Profiles of Chitin and Chitosan Tablets.

dependent on disintegrant type. However, the concentration of some disintegrants affected the tablet hardness whereas some did not. Moreover, as the amount of disintegrant increased, the results varied. For all formulations, the increase of tablet hardness was found with the increasing of compressional force.

Increasing the concentration of chitin and chitosan in the tablet slightly decreased the tablet hardness possibly due to the reduction of interparticulate forces between particles of tablet. The hardness of chitin tablets was slightly greater than that of chitosan at the same concentration and compressional level. This result might be attributable to the greater structural rigidity of chitin due to its acetylamino groups [14]. Chitin and chitosan of different sources exhibited almost the same effect on tablet hardness. As expected, tablet hardness was dependent on compressional force. Greater force produced more dense and less porous tablets, with stronger particle-to-particle bonds which led to harder tablets.

The friability of tablets was less than 0.7 percent for all formulations which was within the acceptable limit (less than 0.8%) [18]. It was also noticed that the friability decreased as the compressional force increased.

TABLE 2
The Hardness and Disintegration Time of Various Paracetamol Formulations Compressed at Two Forces (n=6).

Disintegrant	Hardness (kp)		Disintegration time (sec)	
	600 pounds	900 pounds	600 pounds	900 pounds
Chitin(J) 1.5%	7.9 ± 0.1 *	9.7 ± 0.1	445.0 ± 8.4	506.2 ± 9.1
Chitin(J) 3%	7.9 ± 0.1	9.5 ± 0.1	121.2 ± 2.7	241.0 ± 4.7
Chitin(J) 5%	7.8 ± 0.1	9.4 ± 0.1	91.2 ± 1.1	119.7 ± 1.9
Chitin(J) 7%	7.7 ± 0.1	9.3 ± 0.1	46.5 ± 0.7	60.5 ± 0.8
Chitin(U) 1.5%	7.9 ± 0.1	9.6 ± 0.1	577.7 ± 9.8	699.7 ±12.7
Chitin(U) 3%	7.8 ± 0.1	9.5 ± 0.1	165.8 ± 2.8	386.3 ± 4.2
Chitin(U) 5%	7.8 ± 0.1	9.4 ± 0.1	115.5 ± 1.6	176.5 ± 2.9
Chitin(U) 7%	7.8 ± 0.1	9.4 ± 0.1	41.2 ± 0.8	67.7 ± 1.3
Chitosan(J) 1.5%	7.8 ± 0.1	9.5 ± 0.1	298.3 ± 3.8	498.3 ± 5.6
Chitosan(J) 3%	7.8 ± 0.1	9.4 ± 0.1	140.0 ± 2.5	198.0 ± 3.2
Chitosan(J) 5%	7.7 ± 0.1	9.3 ± 0.1	76.3 ± 1.1	81.0 ± 1.1
Chitosan(J) 7%	7.7 ± 0.1	9.3 ± 0.1	36.2 ± 0.6	39.5 ± 0.6
Chitosan(U) 1.5%	7.9 ± 0.1	9.5 ± 0.1	507.5 ±10.0	644.8 ±12.8
Chitosan(U) 3%	7.7 ± 0.1	9.3 ± 0.1	162.0 ± 3.1	314.8 ± 6.1
Chitosan(U) 5%	7.6 ± 0.1	9.3 ± 0.1	86.3 ± 1.6	133.0 ± 2.5
Chitosan(U) 7%	6.9 ± 0.1	9.1 ± 0.1	53.6 ± 1.3	72.2 ± 1.6
CS	7.4 ± 0.1	9.2 ± 0.1	159.5 ± 3.8	245.0 ± 2.8
SSG	8.3 ± 0.1	10.0 ± 0.1	34.5 ± 0.5	36.8 ± 0.4
CCS	7.6 ± 0.1	9.3 ± 0.1	36.0 ± 0.5	39.5 ± 0.7
MMC	8.1 ± 0.1	9.8 ± 0.1	423.3 ± 8.2	1,746.7 ±24.6

* mean ± S.D.

The disintegration times of tablets made with different disintegrant types and concentrations at various compressional forces are listed in TABLE 2. It was found that increasing the concentration of chitin and chitosan of both sources dramatically decreased the disintegration time. On the contrary, increasing the compressional force prolonged the disintegration. At the concentration level of 7%, tablets containing chitosan(J) exhibited about 35 seconds in disintegration time the

same as tablets containing SSG and CCS and seemed to be faster than other formulations. The disintegration time of tablets containing MCC was the slowest of more than 30 minutes, while tablets containing CS could disintegrate in about 3-4 minutes. It was noted that compressional force slightly affected the disintegration times of tablets containing SSG and CCS, but evidently increased those of other formulations.

Comparison of disintegration among these new disintegrants, as shown in FIGURE 9, indicated that tablets containing chitosan(J) exhibited faster disintegration time followed by chitin(J), chitosan(U) and chitin(U), respectively. The results obtained in disintegration tests corresponded to the observations obtained in moisture sorption of pure disintegrant tablets. In addition, the relationship between the disintegration time and extent of water uptake of paracetamol tablets containing different concentrations of chitin and chitosan after 180 seconds, in FIGURE 10, depicted parabolic relationships except for the tablets containing chitin(U). On a log-log scale, a significant linear correlation was found between the disintegration time and extent of water uptake (log y = -1.2691 log x +0.9221, -1.8890 log x + 0.6138, -1.1970 log x + 0.9478, and r^2 = 0.9757, 0.9050, 0.9656, for chitin(J), chitosan(J) and chitosan(U), respectively). Thus, water uptake seemed to be the step that limited the rate of disintegration for these tablets. Therefore, crystallinity, degree of acetylation, chain length and particle size of these polymers affected the disintegration. Particles of chitin and chitosan swelled and seemed to be relatively potent in tablets. However, the swelling capacity did not evidently relate to the disintegration efficiency. It was found in this study that the possible mechanisms of disintegration of chitin and chitosan related to their moisture sorption and water uptake. However, other mechanisms might additionally correlate to their disintegration action.

The dissolution data of paracetamol tablets compressed at different forces are summarized in TABLE 3. Corresponding to the disintegration result, increasing the concentration of chitin and chitosan markedly increased the drug dissolved while increasing the compressional force showed opposite effect. The effect of compressional force on dissolution was also noticed in all formulations except those containing SSG and CCS. It was noted that tablets containing 5% and 7% of chitin and chitosan, CS, SSG and CCS at both compressional forces in this study were complied to the requirement of US standard, that not less than 80% of the labeled amount of drug was dissolved in 30 minutes. In contrast, formulation of MCC did

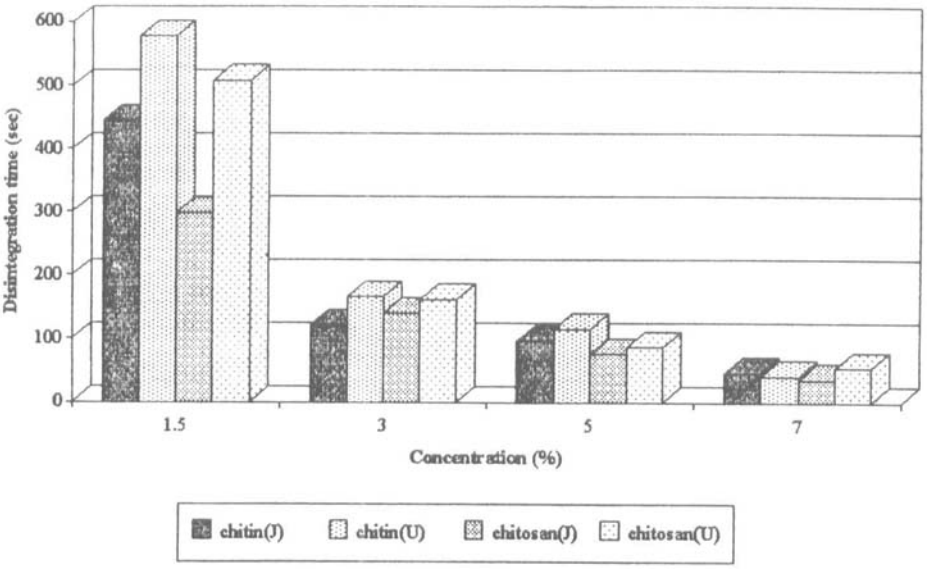

FIGURE 9
Disintegration Times of Paracetamol Tablets Containing Different Concentrations of Chitin and Chitosan and Compressed at 600 Pounds.

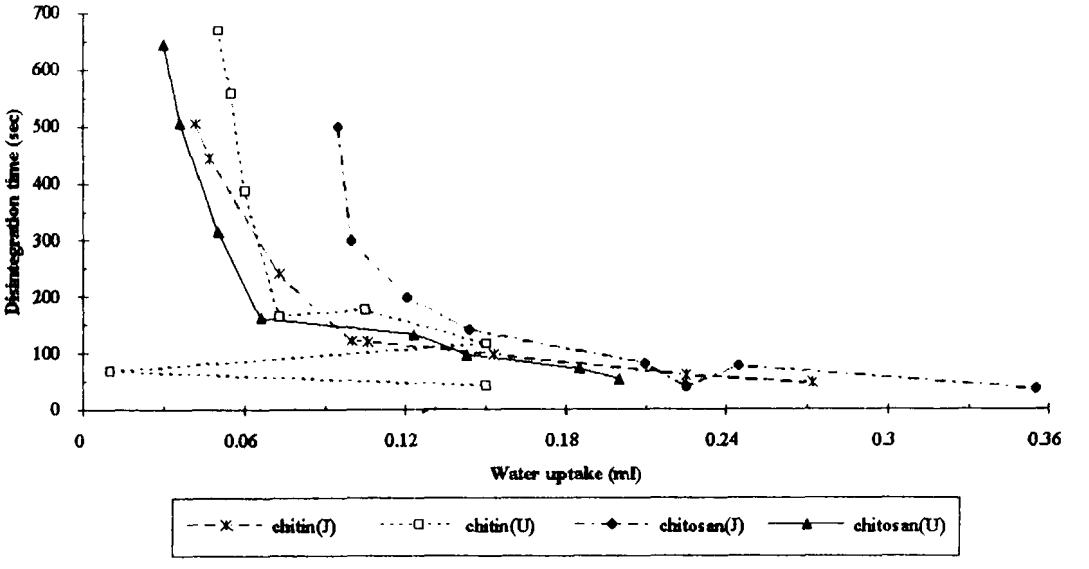

FIGURE 10
Relationships Between Water Uptake and Disintegration Time of Paracetamol Tablets Containing Different Concentrations of Chitin and Chitosan and Compressed at 600 and 900 Pounds.

TABLE 3
Percent Drug Dissolved from Various Paracetamol Formulations Compressed at Two Forces (n=6).

Time	Chitin(J) 1.5%		Chitin(J) 3%		Chitin(J) 5%		Chitin(J) 7%	
(min)	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds
5	7.5 ±1.8 *	7.0±1.6	14.9±1.2	12.4±1.6	31.1±1.8	27.8±1.9	42.6±1.5	38.6±1.9
10	14.9±1.7	13.8±1.6	24.8±1.3	23.7±1.7	45.4±1.6	45.4±1.9	67.3±1.1	60.5±1.7
15	25.6±1.8	21.8±1.2	35.4±1.2	33.5±1.3	73.7±1.5	60.2±1.9	82.9±1.3	79.8±1.8
20	33.6±1.8	32.4±1.2	56.5±1.1	56.0±1.1	81.1±1.3	71.9±1.9	89.7±1.1	85.2±1.4
25	43.9±1.4	40.5±1.2	62.6±1.0	60.6±1.2	89.9±1.3	83.0±1.8	92.6±1.1	90.1±1.4
30	49.5±1.1	47.7±1.2	71.2±1.1	69.3±1.1	95.5±1.2	94.4±1.7	96.2±1.3	95.6±1.3

Time	Chitin(U) 1.5%		Chitin(U) 3%		Chitin(U) 5%		Chitin(U) 7%	
(min)	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds
5	3.6±1.7	3.2±1.7	9.7±1.7	7.5±1.8	28.6±1.8	25.1±1.8	37.7±1.6	30.4±1.7
10	8.7±1.8	8.1±1.8	18.6±1.7	17.2±1.8	44.5±1.6	40.5±1.6	58.6±1.6	54.9±1.6
15	15.6±1.6	15.0±1.8	30.7±1.6	28.8±1.9	66.3±1.5	63.4±1.6	75.1±1.5	70.1±1.6
20	24.3±1.6	22.3±1.6	43.0±1.4	41.7±1.6	82.7±1.4	78.3±1.6	85.8±1.3	85.0±1.3
25	29.9±1.4	29.2±1.4	58.0±1.2	54.4±1.2	88.2±1.4	85.5±1.2	92.0±1.0	92.1±1.1
30	34.6±1.3	32.8±1.3	66.0±1.1	63.0±1.2	95.2±1.2	93.2±1.2	95.9±1.0	96.0±1.0

Time	Chitosan(J) 1.5%		Chitosan(J) 3%		Chitosan(J) 5%		Chitosan(J) 7%	
(min)	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds
5	8.1±1.7	7.1±1.8	14.1±1.6	13.2±1.8	33.3±2.0	30.8±2.0	47.4±1.5	42.9±1.7
10	14.5±1.7	12.7±1.7	26.5±1.6	23.0±1.4	51.0±1.9	46.9±1.6	76.4±1.4	75.0±1.2
15	23.7±1.5	23.4±1.6	36.9±1.7	33.5±1.2	73.9±1.4	69.0±1.6	88.3±1.3	85.3±1.2
20	30.5±1.3	28.7±1.4	49.7±1.7	48.5±1.2	81.7±1.5	80.6±1.4	93.6±1.1	92.0±1.1
25	36.0±1.3	33.1±1.4	61.3±1.4	60.1±1.3	89.2±1.4	87.0±1.3	94.7±1.3	94.9±1.2
30	45.3±1.2	41.3±1.3	73.8±1.2	71.7±1.1	94.9±1.1	94.8±1.2	96.1±1.2	96.2±1.0

Time	Chitosan(U) 1.5%		Chitosan(U) 3%		Chitosan(U) 5%		Chitosan(U) 7%	
(min)	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds
5	5.4±1.8	4.3±2.0	12.0±1.7	11.0±2.0	37.2±1.7	34.5±2.0	45.4±1.5	42.5±1.5
10	13.8±1.6	12.6±1.8	23.7±1.8	18.5±1.6	46.9±1.5	46.2±1.9	73.1±1.1	67.7±1.3
15	21.5±1.3	20.7±1.5	35.3±1.6	29.9±1.4	65.1±1.3	64.2±1.7	80.4±1.3	80.7±1.3
20	28.9±1.5	26.6±1.7	47.7±1.5	40.0±1.4	81.4±1.2	81.4±1.5	92.3±1.3	92.3±1.2
25	36.3±1.4	34.5±1.4	58.6±1.4	53.3±1.2	88.7±1.1	89.5±1.4	94.4±1.1	95.0±1.2
30	48.5±1.1	45.2±1.2	69.4±1.4	65.0±1.1	95.0±1.2	95.4±1.2	96.1±1.1	96.7±1.1

Time	CS		SSG		MMC		CCS	
(min)	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds
5	33.4±1.8	28.5±1.8	61.1±1.3	60.1±1.6	5.4±1.5	4.1±1.3	61.3±1.9	60.0±1.6
10	49.2±1.5	47.8±1.7	81.1±1.3	78.8±1.3	8.6±1.3	6.9±1.3	76.7±1.8	76.9±1.5
15	79.6±1.6	69.8±1.6	90.3±1.2	87.9±1.3	14.9±1.4	11.5±1.2	90.2±1.8	89.6±1.5
20	84.8±1.4	83.4±1.6	92.3±1.1	93.0±1.2	89.4±1.2	18.9±1.1	92.6±1.7	91.2±1.3
25	89.8±1.0	90.1±1.2	93.9±1.0	93.9±1.2	29.4±1.0	24.7±1.1	94.1±1.4	93.6±1.2
30	94.6±1.0	94.4±1.1	96.5±1.0	96.3±0.9	33.8±1.0	30.2±1.1	97.0±1.4	95.6±1.1

* mean ± S.D.

not pass the limit of the US standard, the same as formulations of 1.5 and 3% of chitin and chitosan. Comparison of dissolution among tablets containing chitin and chitosan from both sources at the same concentration and compressional force indicated that the percentage of drug dissolved decreased in the following order: chitosan(J) > chitosan(U) > chitin(J) > chitin(U). Difference between sources of polymers in drug dissolved from tablets containing 5 and 7% of chitin and chitosan compressed at two different forces was found only at the initial time. Formulations containing 7% of chitosan from both sources exhibited the highest drug dissolved and quite similar to those containing SSG and CCS except at the first 5 minutes. Statistical analysis revealed that there was no significant difference in drug dissolved between tablets containing SSG, CCS and 7% of chitosan of both sources at the same compressional force ($p<0.05$) as depicted in FIGURE 11. In addition, tablets containing 7% chitin(J) also showed no significant difference in dissolution from tablets containing SSG at compressional force of 600 pounds ($p<0.05$).

It could be noticed that the dissolution of tablets containing chitin and chitosan was not correspondingly related to their disintegration. However, it seemed to relate to their swelling capacity. This could be explained that highly swollen particles should normally have greater porosity. Since chitin and chitosan were not soluble but swelled in water and likely to behave the same in dissolution medium (pH 5.8 phosphate buffer solution), the release of dissolved drug from insoluble matrix was diffusion through the openings created by the porosity of the matrix as described by Higuchi square root equation [19]. Greater porosity indicated greater release of the drug molecule. Therefore, particles of higher swelling capacity released greater amount of drug.

4. Stability Study.

After storage in 75% relative humidity at 45°C for 5 days, an increase of 3-4 kiloponds in hardness value was surprisingly found in all formulations of both compressional forces, particularly formulation containing microcrystalline cellulose as shown in TABLE 4. The effect of type and concentration of chitin and chitosan was the same effect as at the initial stage. The friability of all tablets correspondingly decreased after aging to less than 0.5%. This result confirmed that of hardness.

The disintegration of tablets was mostly prolonged, as shown in TABLE 4, but the dissolution of drug was slightly decreased, as displayed in TABLE 5, after

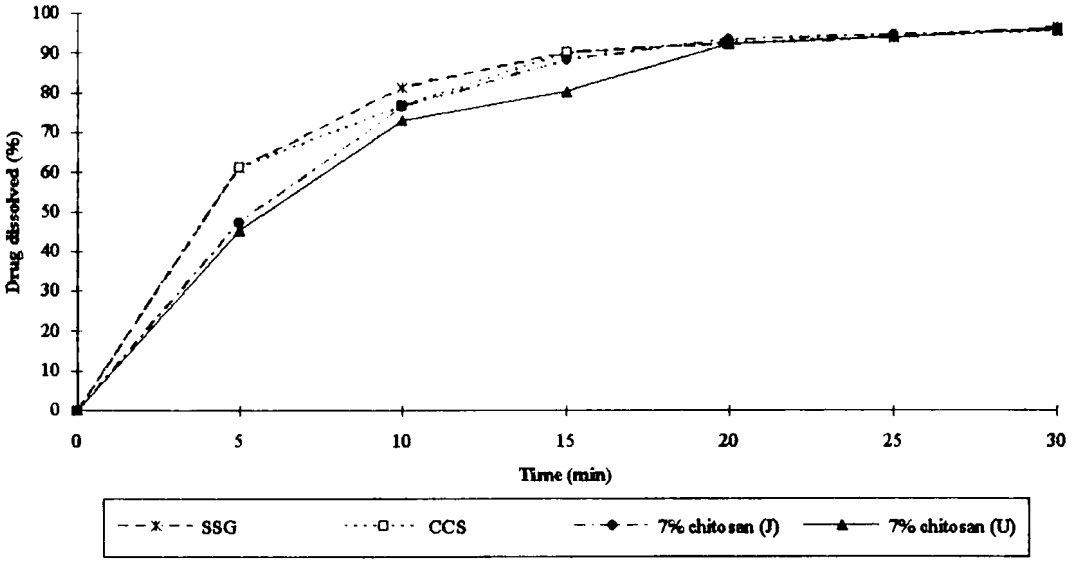

FIGURE 11
Dissolution Profiles of Paracetamol Tablets Containing 7% Chitosan, SSG and CCS Compressed at 600 Pounds.

aging. Accelerated conditions had less effect on the disintegration time and drug dissolution of tablets containing ≥ 5% of chitin and chitosan than those containing < 5%. Tablets containing SSG were slightly affected followed by tablets containing CCS. Tablets containing CS and MCC were highly affected. Statistical analysis indicated that after aging tablets containing 7% of chitosan of both sources still showed no significant difference in dissolution from tablets containing SSG at the same compressional force. In addition, the dissolution profiles of those containing 7% chitin from both sources were non significantly different from that of CCS ($p < 0.05$) at the same compressional force, as depicted in FIGURE 12. It could be stated that aging slightly affected the dissolution of tablets containing chitin and chitosan of higher concentration the same as those containing SSG and CCS.

CONCLUSION

Chitin and chitosan showed to be effective disintegrants if used in the concentration of ≥5%. Chitosan was more effective than chitin. Different sources

TABLE 4
The Hardness and Disintegration Time of Various Paracetamol Formulations Compressed at Two Forces after Aging (n=6).

Disintegrant	Hardness (kp)		Disintegration time (sec)	
	600 pounds	900 pounds	600 pounds	900 pounds
Chitin(J) 1.5%	11.3 ± 0.2 *	13.7 ± 0.1	860.7 ±12.7	1,325.0 ±20.8
Chitin(J) 3%	11.2 ± 0.1	13.6 ± 0.1	319.0 ± 6.0	575.0 ±12.1
Chitin(J) 5%	11.2 ± 0.1	13.5 ± 0.1	152.8 ± 2.5	203.3 ± 2.4
Chitin(J) 7%	11.2 ± 0.1	13.5 ± 0.1	70.8 ± 1.0	134.3 ± 1.7
Chitin(U) 1.5%	11.0 ± 0.1	13.6 ± 0.2	934.2 ±19.6	1,359.2 ±23.6
Chitin(U) 3%	11.4 ± 0.1	13.6 ± 0.1	507.8 ± 6.5	872.5 ±10.3
Chitin(U) 5%	11.3 ± 0.1	13.4 ± 0.1	175.0 ± 2.1	319.2 ± 4.0
Chitin(U) 7%	11.2 ± 0.1	13.4 ± 0.2	72.3 ± 1.3	136.7 ± 2.1
Chitosan(J) 1.5%	11.2 ± 0.1	13.4 ± 0.2	506.7 ± 7.1	1,065.3 ±12.0
Chitosan(J) 3%	11.0 ± 0.1	13.4 ± 0.2	290.0 ± 4.4	405.8 ± 6.7
Chitosan(J) 5%	11.0 ± 0.1	13.3 ± 0.1	104.3 ± 1.5	123.0 ± 1.7
Chitosan(J) 7%	10.9 ± 0.1	13.1 ± 0.1	53.3 ± 0.7	79.2 ± 1.2
Chitosan(U) 1.5%	11.1 ± 0.1	13.4 ± 0.2	997.5 ±20.9	1,342.9 ±25.7
Chitosan(U) 3%	10.9 ± 0.1	13.4 ± 0.2	375.8 ± 6.8	925.3 ±17.9
Chitosan(U) 5%	11.0 ± 0.1	13.3 ± 0.2	200.8 ± 3.7	313.8 ± 5.8
Chitosan(U) 7%	11.3 ± 0.1	14.2 ± 0.2	77.3 ± 1.5	134.5 ± 2.0
CS	10.2 ± 0.1	13.3 ± 0.1	340.8 ± 8.3	447.0 ±12.6
SSG	10.9 ± 0.1	13.1 ± 0.1	56.2 ± 0.9	60.8 ± 0.9
CCS	10.3 ± 0.1	13.7 ± 0.2	52.0 ± 0.8	71.7 ± 0.9
MMC	11.8 ± 0.1	13.9 ± 0.2	784.3 ±14.4	>1,800

* mean ± S.D.

of polymers exhibited different effectiveness. Crystallinity, degree of acetylation chain length and particle size seemed to affect their efficiency. They were better disintegrants than corn starch and microcrystalline cellulose. Tablets containing 7% of chitosan exhibited the same dissolution as tablets containing sodium starch glycolate and croscarmellose sodium. Moisture sorption and water uptake were found to be the mechanisms of disintegration while dissolution was more related to

TABLE 5

Percent Drug Dissolved from Various Paracetamol Formulations Compressed at Two Forces after Aging (n=6).

Time	Chitin(J) 1.5%		Chitin(J) 3%		Chitin(J) 5%		Chitin(J) 7%	
(min)	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds
5	6.7±1.9 *	6.01.9	12.2±1.4	11.1±1.7	27.8±1.8	23.2±1.9	38.8±1.7	32.4±2.2
10	13.7±1.7	12.31.8	23.9±1.3	21.2±1.3	45.4±1.4	38.0±2.0	52.3±1.5	48.5±1.9
15	21.0±1.8	20.41.5	32.6±1.2	31.2±1.3	60.2±1.6	58.8±1.8	67.6±1.3	64.3±1.5
20	30.8±1.2	29.01.4	52.2±1.3	46.7±1.2	71.9±1.4	76.1±1.7	83.1±1.3	77.9±1.5
25	38.7±1.3	36.31.3	59.7±1.2	55.8±1.2	83.0±1.2	84.0±1.6	88.5±1.2	88.0±1.4
30	47.9±1.1	43.61.2	67.5±1.1	63.9±1.0	91.8±1.4	90.7±1.7	95.7±1.2	95.0±1.1

Time	Chitin(U) 1.5%		Chitin(U) 3%		Chitin(U) 5%		Chitin(U) 7%	
(min)	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds
5	2.8±1.8	2.8±1.8	6.5±1.9	6.0±1.7	23.7±1.7	22.7±1.9	30.4±1.7	25.7±1.9
10	7.4±1.9	6.2±1.6	16.1±1.8	15.9±1.8	40.2±1.5	34.6±1.9	53.2±1.7	45.4±1.6
15	11.3±1.6	10.6±1.5	25.0±1.5	25.6±1.7	61.9±1.6	57.8±1.5	70.9±1.6	66.8±1.6
20	16.8±1.4	17.5±1.5	37.8±1.5	38.1±1.6	71.5±1.3	68.6±1.5	85.8±1.4	79.0±1.4
25	23.7±1.5	23.3±1.3	51.6±1.3	50.7±1.4	83.1±1.2	80.1±1.5	92.3±1.3	90.3±1.4
30	29.1±1.4	27.2±1.2	63.5±1.2	61.6±1.6	91.7±1.2	89.8±1.3	95.6±1.3	95.1±1.1

Time	Chitosan(J) 1.5%		Chitosan(J) 3%		Chitosan(J) 5%		Chitosan(J) 7%	
(min)	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds
5	7.6±1.1	6.4±1.7	11.1±1.9	10.3±1.6	28.2±1.8	27.2±1.7	43.8±1.9	40.1±1.9
10	11.8±1.3	10.4±1.8	23.4±1.8	20.7±1.5	46.3±1.6	43.8±1.6	69.1±1.4	70.1±1.6
15	22.1±1.1	19.3±1.2	33.9±1.5	30.8±1.6	68.7±1.3	67.0±1.6	86.4±1.2	83.4±1.4
20	28.1±1.1	23.7±1.3	48.6±1.6	44.6±1.4	79.4±1.5	77.5±4.5	89.4±1.3	89.4±1.3
25	33.5±1.1	31.7±1.1	60.0±1.3	58.2±1.1	86.7±1.2	85.0±1.2	94.1±1.3	93.6±1.5
30	42.8±1.0	40.1±1.1	69.6±1.1	66.9±1.0	94.4±1.2	93.6±1.3	96.2±1.2	95.7±1.2

Time	Chitosan(U) 1.5%		Chitosan(U) 3%		Chitosan(U) 5%		Chitosan(U) 7%	
(min)	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds
5	5.0±1.8	3.7±2.0	10.2±2.3	7.0±1.9	22.5±1.9	21.5±1.8	37.9±1.8	32.0±1.8
10	12.5±1.7	11.3±1.8	18.9±1.9	14.2±1.9	37.8±1.5	32.2±1.7	62.7±1.6	58.9±1.7
15	18.6±1.5	17.0±1.7	29.8±1.6	23.6±1.5	58.2±1.4	49.4±1.8	78.7±1.4	78.9±1.3
20	25.4±1.5	24.6±1.7	40.5±1.6	33.1±1.4	73.6±1.3	69.8±1.5	89.9±1.2	90.3±1.4
25	34.4±1.4	32.6±1.6	52.6±1.6	46.8±1.3	84.4±1.3	82.0±1.3	94.0±1.1	93.2±1.3
30	45.3±1.2	40.7±1.5	64.5±1.6	62.0±1.0	92.1±1.1	91.9±1.3	95.9±1.1	95.8±1.0

Time	CS		SSG		MMC		CCS	
(min)	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds	600 pds	900 pds
5	18.0±2.1	12.8±1.8	59.5±1.2	57.8±1.4	4.6±1.2	3.8±1.3	38.1±1.5	34.7±1.6
10	33.1±1.5	23.8±1.7	78.6±1.2	78.1±1.3	7.0±1.3	5.9±1.8	57.1±1.4	57.0±1.5
15	50.0±1.6	32.9±1.6	88.7±1.2	88.3±1.1	12.6±1.1	10.5±1.1	74.3±1.3	74.2±1.5
20	59.5±1.4	48.7±1.6	92.3±1.0	92.3±1.2	22.0±1.2	17.2±1.1	86.6±1.3	85.5±1.4
25	71.3±1.0	60.0±1.3	94.3±1.1	93.8±1.0	26.8±1.1	22.4±1.1	91.5±1.2	90.6±1.1
30	78.8±1.1	70.4±1.1	96.3±0.9	95.9±1.1	30.6±1.1	26.9±1.0	94.5±1.1	94.7±1.0

* mean ± S.D.

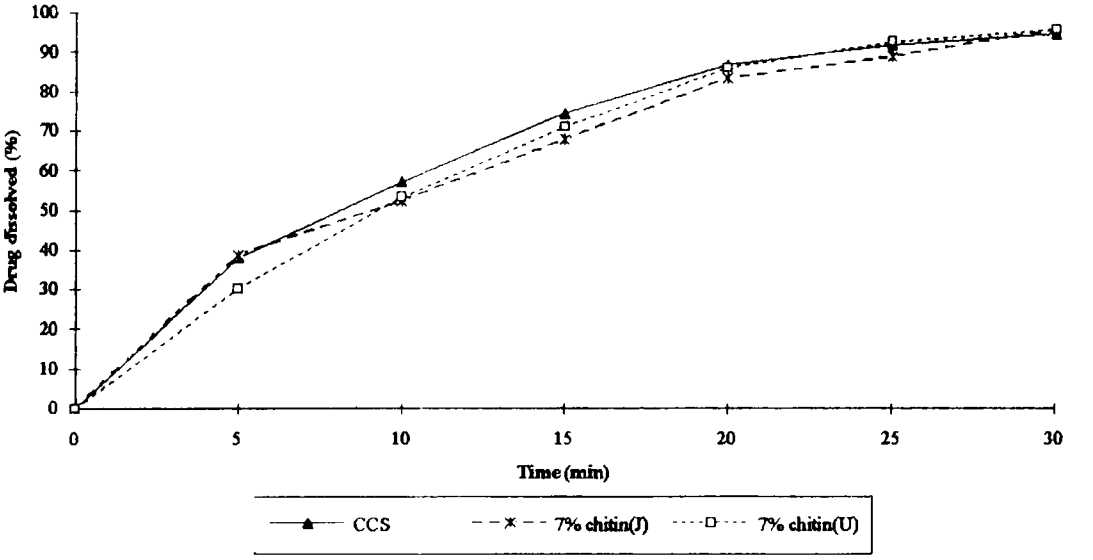

FIGURE 12
Dissolution Profiles of Paracetamol Tablets Containing 7% Chitin and CCS Compressed at 600 Pounds, After Aging.

swelling capacity. Aging slightly affected the disintegration and dissolution efficiency.

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