April 1, 2009

A Novel Pregelatinized Starch as a Sustained-Release Matrix Excipient

By Masaaki Endo,Kazuhiro Obae,Yoshihito Yaginuma

The authors examine the use of a novel highly functional pregelatinized starch as a controlled-release matrix excipient.

Hydrophilic gel-forming matrix systems are widely used in oral controlled-release dosage forms. Hydrophilic polymer hydrates form a viscous gel layer around the tablet surface, and drug release is controlled in a sustained manner by diffusion through a gel layer and the erosion of the gel (1). Drug solubility, however, greatly affects the rate of diffusion and erosion. It is especially difficult to control the release rate of highly water-soluble and insoluble drugs (2–4). Moreover, various gastrointestinal factors such as ionic strength and mechanical destructive force also affect the drug-release rate (5–8). To solve these problems or predict these influences, many studies have examined factors affecting drug release.

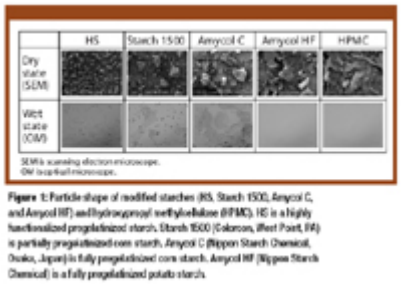

Figure 1 (All figures are courtesy of the authors.)

In this study, a highly functional pregelatinized starch (HS) was investigated as the potential basis for developing a hydrophilic matrix system for sustained release (9). The influence of drug solubility and external factors such as ionic strength, mechanical force, and accelerated storage conditions on the drug-release rate was evaluated. In addition, the effect of polyethylene glycol (PEG) on drug-release profiles was investigated to obtain zero-order release profiles.

HS was prepared by controlled thermal pregelatinization of potato starch and a spray-drying technique. It is compatible with the *National Formulary, European Pharmacopoeia,* and *Japanese Pharmaceutical Excipients.* The properties of HS are shown in Table I. HS has different properties from conventional pregelatinized starches and conventional hydrophilic gel-matrix excipients because of its high viscosity and insoluble element in dissolution media (see Figure 1).

Table I: Basic properties of modified starches and hydroxypropyl methylcellulose (HPMC).

	HS	Starch 1500	Amycol C	Amycol HF	HPMC
Average particle diameter (μm)	32	53	57	59	48
Bulk density (g/cm³)	0.27	0.56	0.36	0.34	0.28
Angle of repose (°)	36	40	42	40	44
Viscosity (mPa · s)	75	11	7	137	69
Water-soluble content (%)	73	11	35	100	100

HS is a highly functional pregelatinized starch. Starch 1500 (Colorcon, West Point, PA) is partially pregelatinized corn starch. Amycol C (Nippon Starch Chemical, Osaka, Japan) is fully pregelatinized corn starch. Amycol HF (Nippon Starch Chemical) is pregelatinized potato starch.

Table 1

Experimental methods

Materials. *Model drugs.* Ethenzamide (ETZ), acetaminophen (APAP), and sodium salicylic acid (SSA) were used as model drugs and may be characterized as

water-insoluble, moderately water-soluble, and highly water-soluble drugs, respectively. All drugs were purchased from Yoshitomi Pharmaceutical (Tokyo).

Matrix excipients. HS was prepared by Asahi Kasei Chemicals (Tokyo). Hydroxypropyl methylcellulose [(HPMC) Metolose 90SH-100SR, Metolose 90SH-4000SR, Metolose 10000SR] was purchased from Shin-Etsu Chemical (Tokyo).

Other excipients. Partially pregelatinized corn starch (Starch 1500) was purchased from Colorcon (West Point, PA). Fully pregelatinized corn starch (Amycol C) and fully pregelatinized potato starch (Amycol HF) were purchased from Nippon Starch Chemical (Osaka, Japan). Microcrystalline cellulose (MCC), Ceolus KG-802, was manufactured by Asahi Kasei Chemicals. PEG (Macrogol 6000) was supplied by Sanyo Chemical (Kyoto, Japan). Sorbitol (Sorbitol SP) was purchased from Kowa Pharmaceutical (Nagoya, Japan).

Evaluation of properties of modified starches and HPMC. *Average particle diameter.* Measurement samples of 5 g were sieved for 5 min using an air-jet JIS sieve of 20, 38, 75, and 150 μm-mesh. The weight percent remaining on each sieve after sieving was calculated, and the particle diameter was calculated as the cumulative weight percent of 50%.

Water-soluble content. Sample dispersions of 1% were prepared at 20 °C and were centrifuged for 15 min at 5000 G. The supernatant was dried at 105 °C until a constant weight was reached. The dry weight was defined as the amount of soluble content and was expressed as a percentage of the initial weight of the samples.

Viscosity. The viscosity of 2% sample dispersions was determined at 25 °C with a rotary viscometer (TVB-10, Toki Sangyo, Tokyo) using an M1 body.

*Preparation of matrix tablets*A model drug, a matrix excipient, and other excipients were physically admixed. The mixtures of 180 mg were compressed using an 8.0-mm diameter round-faced punch at compression pressure of 60 MPa.

Drug-release study. The dissolution tests were carried out at 37 °C ± 0.5 °C using a USP Type 1 apparatus or a USP Type 2 apparatus rotating from 50 to 200 rpm. The test media consisted of 900 mL of second fluid of the *Japanese Pharmacopoeia* (14th edition) (JP-2, pH 6.8, and ionic strength 0.14 M) and McIlvaine buffer (pH 7.2 and ionic strength 0.39 M).

Stability test under accelerated conditions. Dissolution profiles and the yellowness index (YI) of HS and HPMC matrix tablets were evaluated after storage at 40 °C and 75% relative humidity (RH) in sealed glass bottles, and at 60 °C in polyamine–polyethylene bags. The YI was measured by a spectrophotometer (SE200, Nippon Denshoku, Tokyo).

Results and discussion

Preliminary screening of matrix excipients: influence of α-amylase in dissolution media. Several thermally modified starches were investigated as matrix-forming excipients for sustained-release tablets (10–14). These studies pointed out that only fully pregelatinized starches functioned for the purpose of forming matrices because of their high gelling capacities (11, 13, 14). However, it was reported that matrix tablets with fully pregelatinized starch could not provide stable drug-release profiles when α-amylase was added in test media to mimic the gastrointestinal environment (11).

The influence of α-amylase on drug release from HS matrix tablets was investigated and compared with commercially available partially and fully pregelatinized starches. Four different tablets, composed of APAP, MCC, and modified starch (HS, Starch 1500, Amycol C, and Amycol HF) were tested.

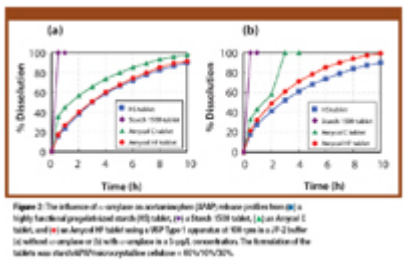

Figure 2

Figure 2 shows the dissolution profiles of APAP from various starch matrix tablets (starch/APAP/MCC = 60%/10%/30%) in different two buffers, JP-2 buffer without α-amylase (see Figure 2a) and JP-2 buffer with α-amylase in a 5-g/L concentration (see Figure 2b). The activity of α-amylase was adjusted to 1700 IU/L, which is close to the median α-amylase activity in pancreatic juice (11).

Matrix tablets made of conventional partially pregelatinized corn starch disintegrated completely within 0.5 h, and sudden APAP release occurred. For both fully pregelatinized starches, sustained- release profiles were obtained in media without α-amylase. However, the drug-release rate from the fully pregelatinized starch matrix changed faster in media containing α-amylase. These results were the same phenomenon as described in previous work (11). On the other hand, matrix tablets made of HS were well controlled in the same way, with or without α-amylase. This situation can be explained by the high gel-forming ability of HS with high viscosity to prevent the dissolution and by the high resistance to α-amylase based on its degree of pregelatinization. HS has the same viscosity as HPMC and the moderate degree of pregelatinization between conventional partially pregelatinized starches and fully gelatinized starches (see Table I) contributes to its good balance of resistance to α-amylase and the gel-forming ability.

Based on this prescreening test, the following evaluations were done with HS and HPMC as matrix excipients: a dissolution study under high ionic-strength conditions, a dissolution study under high mechanical-force conditions, a zero-order release, and a storage stability of dissolution profiles and of tablet color.

Dissolution study under high ionic-strength conditions. The influence of ionic strength of dissolution media on APAP release rate was investigated. HS or HPMC matrix tablets containing APAP and MCC were prepared (HS or HPMC/APAP/MCC = 60%/ 10%/30%) and tested for dissolution using two media of different ionic strength: JP-2 buffer (ionic strength 0.20 M) and McIlvaine buffer (ionic strength 0.39 M).

Figure 3 shows the release profiles of APAP from HS and HPMC matrix tables. The release profiles of APAP from HS matrix tablets hardly changed between the JP-2 buffer and the McIlvaine buffer, but the profiles of HPMC were largely influenced by ionic strength. The HPMC matrix tablet couldn't maintain its matrix structure at high ionic-strength conditions, and burst release of APAP occurred. These results were caused by the difference in swelling ability in high-ionic-strength conditions. In the case of HPMC, as the ionic strength increases, the degree of swelling attributable to hydration decreases because the amount of water available to hydrate HPMC was reduced when more water is required to keep the ions in solution (5). In contrast, HS has a lot of hydroxyl groups on its backbone, so HS could hydrate in high ionic-strength conditions without competing with electrolytes.

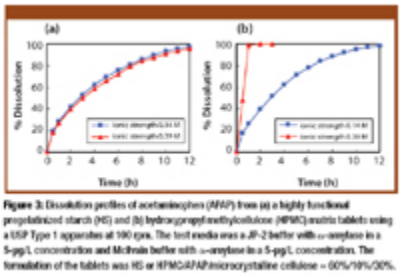

Figure 3

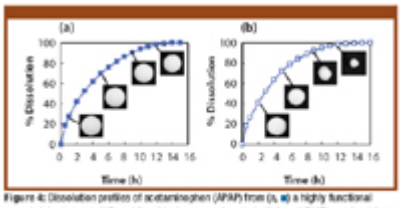

Figure 4

Dissolution study under high mechanical-force conditions. The influence of mechanical force at different rotation speeds on the APAP release rate was investigated. Figure 4 shows dissolution profiles of APAP from HS or HPMC matrix tablets (HS or HPMC/APAP /MCC = 60%/10%/30%). The experiments were performed using a USP Type 1 apparatus at a rotation speed of 100 rpm in a JP-2 buffer containing α-amylase in a 5-μg/L concentration. Under these conditions, the release rates of APAP from the HS tablet and the HPMC tablet were almost identical, but the drug-release mechanisms were different. HS matrix tablets were hardly eroded, whereas HPMC matrix tablets gradually became smaller by erosion.

Figure 5 shows the dissolution profiles of APAP of HS or HPMC matrix tablets (HS or HPMC/APAP/MCC = 60%/10%/30%). The experiments were performed using a USP Type 2 apparatus at rotation speeds of 50 or 200 rpm in a JP-2 buffer containing α-amylase in a 5-μg/L concentration. Under these conditions, the drug-release profiles of HPMC were remarkably accelerated by increasing rotation speed. On the other hand, those of HS matrix tablets were hardly affected by rotation speed. The difference of 85% APAP release time between 50 and 200 rpm of HPMC and HS were respectively 3.4 h and 0.9 h.

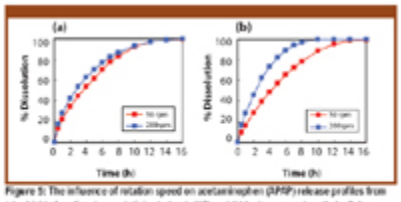

Figure 5

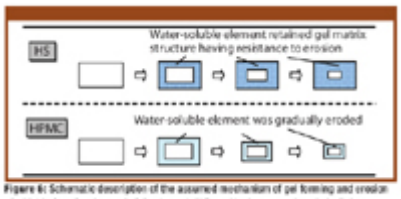

Figure 6

Figure 6 is a schematic description of gelling and drug release of HS and HPMC matrix tablets in dissolution tests. The HS matrix tablets could retain the gel matrix structure with resistance to erosion because the swollen particles of HS did not entirely dissolve and maintain the gel-matrix structure. On the other hand, the HPMC gel layer of the tablet surface was gradually eroded because HPMC particles dissolved completely and could not maintain gel structure. Therefore, the rate of dissolution was accelerated by rapid paddle rotation.

Zero-order release. The effects of PEG on drug-release profiles were investigated to make the formulation of zero-order release matrix tablets. HS or HPMC matrix tablets containing various model drugs (ETZ, APAP, and SSA) with or without PEG, were used in this study.

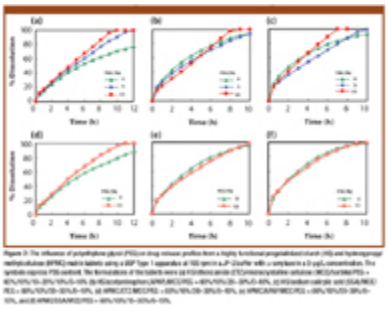

Figure 7

Table II: The formulations of tablets.

	Components	Tablet a	Tablet b	Tablet c	Tablet d	Tablet e	Tablet f
Matrix excipient	HS	60%	60%	60%	-	-	-
	HPMC	-	-	-	60%	60%	60%
Model drug	ETZ	10%	-	-	10%	-	-
	APAP	-	10%	-	-	10%	-
	SSA	-	-	10%	-	-	10%
Other excipients	MCC	10–20%	20–30%	20–30%	20–30%	20–30%	15–30%
	Sorbitol	10%	-	-	-	-	-
	PEG	0–10%	0–10%	0–10%	0–10%	0–10%	0–15%

HS is a highly functionalized pregelatinized starch. HPMC is hydroxypropyl methylcellulose. ETZ is ethenzamide. APAP is acetaminophen. SSA is sodium salicylic acid. MCC is microcrystalline cellulose. PEG is polyethylene glycol.

Table 2

Figure 7 shows the dissolution profiles of model drugs from HS and HPMC matrix tablets. Table II shows the formulations of the tablets. The experiments were performed using a USP Type 1 apparatus at a rotation speed of 100 rpm in a JP-2 buffer containing α-amylase in a 5-μg/L concentration. For HS matrix tablets, HS could control the drug-release profiles from first-order to zero-order depending on PEG concentration, regardless of drug solubility. In contrast, HPMC tablets could not provide zero-order release, especially in the case of water-soluble drugs.

Figure 8 shows the change of tablet weight (see Figure 8a) and water-absorbing capacity (see Figure 8b). The water-absorbing capacity was calculated as a percentage by comparing the tablet weight in the wet state due to water absorption with the tablet weight in the dry state after drying. During 0–2 h, these matrix tablets absorbed a lot of water, and their weights increased. After 2 h, the weights of matrix tablets began to decrease in spite of keeping water absorption. The HS tablet with PEG remarkably absorbed water and lost its weight because the strength of its gel structure weakened.

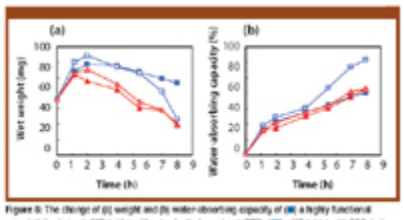

Figure 8

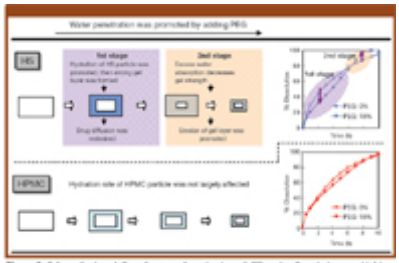

Figure 9

Figure 9 is a schematic description of the assumed mechanism of different actions between HS and HPMC matrix tablets caused by promotion of water penetration into tablets by adding PEG. In the case of HS, in the first stage at 0.5–5 h, the hydration of HS particles was promoted, and a strong gel layer was formed, which contributed to the restraint of drug diffusion. In the second stage of 6 h and after, excess water absorption occurred because the HS water-insoluble elements absorbed a lot of water without dissolving, which contributed to decrease gel strength and to promote gel erosion. Accordingly, the drug-release profiles inclined to zero-order release. In the case of HPMC, the hydration rate of the HPMC particles was not largely affected by adding PEG because the hydration rate was originally rapid. Therefore, the drug-release profiles remained first order regardless of adding PEG.

Storage stability study of dissolution profiles and of tablets color. HS or HPMC matrix tablets containing APAP and MCC with or without PEG were used in this study. Table III shows the formulations of the tablets. These tablets were stored at 40 °C and 75% RH in sealed glass bottles and at 60 °C in polyamine–polyethylene bags.

Table III: The formulations of tablets.

	Components	Tablet a	Tablet b	Tablet c	Tablet d
Matrix excipient	HS	60%	60%	-	-
	HPMC	-	-	60%	60%
Model drug	APAP	10%	10%	10%	10%
Other excipients	MCC	30%	20%	30%	20%
	PEG	-	10%	-	10%

HS is a highly functionalized prepalatinized starch HPMC is hydroxypropyl methylcellulose. APAP is acetaminophen. MCC is microcrystalline cellulose. PEG is polyethylene glycol.

Table 3

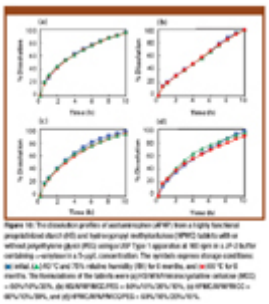

Figure 10 shows the dissolution profiles at the initial state and after storage for 6 months. The dissolution tests were performed using a USP Type 1 apparatus at a rotation speed of 100 rpm in a JP-2 buffer containing α-amylase in a 5-μg/L concentration. For HS matrix tablets, no significant change in release profiles was observed. In contrast, those of HPMC changed under the same conditions.

Figure 11

Figure 11 shows the change of YI. Under conditions of 40 °C and 75 % RH, the YI of the HS matrix tablets slightly changed, although that of HPMC remarkably increased. At 60 °C, the YI of both increased, but the YI of the HS matrix tablets after 6 months was the same level with the initial YI of HPMC tablets. In addition, the YI of the HPMC matrix with PEG remarkably increased.

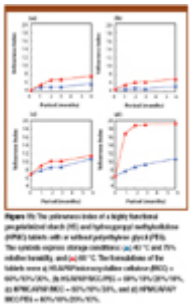

Figure 12

Conclusion

The authors conclude that HS can be applied for the development of sustained-release tablets. Experimental data confirmed the following points:

- Drug release from HS matrix tablets was well controlled under conditions of high ionic strength and high mechanical force
- The zero-order drug-release profile can be obtained by using a mixture of HS and PEG and is independent from drug solubility

- The HS matrix tablets show stable drug-release profiles even under accelerated conditions
- HS is a new matrix excipient that can control drug-release profiles from first- to zero-order sustained release and enables drug release independent of drug solubility and external conditions.

Masaaki Endo is an engineer, **Kazuhiro Obae*** is a chief engineer, and **Yoshihito Yaginuma** is a general manager, all in the Ceolus Research and Development Department at Asahi Kasei Chemicals Corporation, 1-105 Kanda Jinbocho, Chiyoda-ku, Tokyo 101-8101 Japan, obae.kb@om.asahi-kasei.co.jp [http://mailto:obae.kb@om.asahi-kasei.co.jp]

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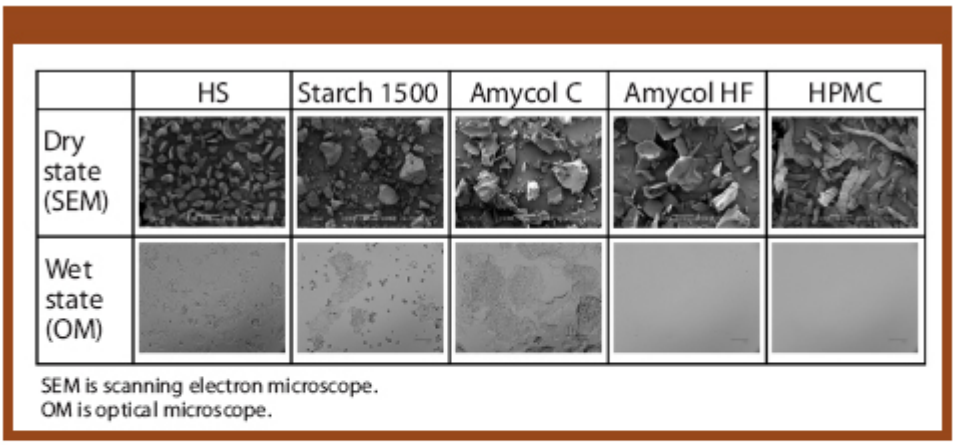

Figure 1: Particle shape of modified starches (HS, Starch 1500, Amycol C, and Amycol HF) and hydroxypropyl methylcellulose (HPMC). HS is a highly functionalized pregelatinized starch. Starch 1500 (Colorcon, West Point, PA) is partially pregelatinized corn starch. Amycol C (Nippon Starch Chemical, Osaka, Japan) is fully pregelatinized corn starch. Amycol HF (Nippon Starch Chemical) is a fully pregelatinized potato starch.

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Figure 1 (All figures are courtesy of the authors.)

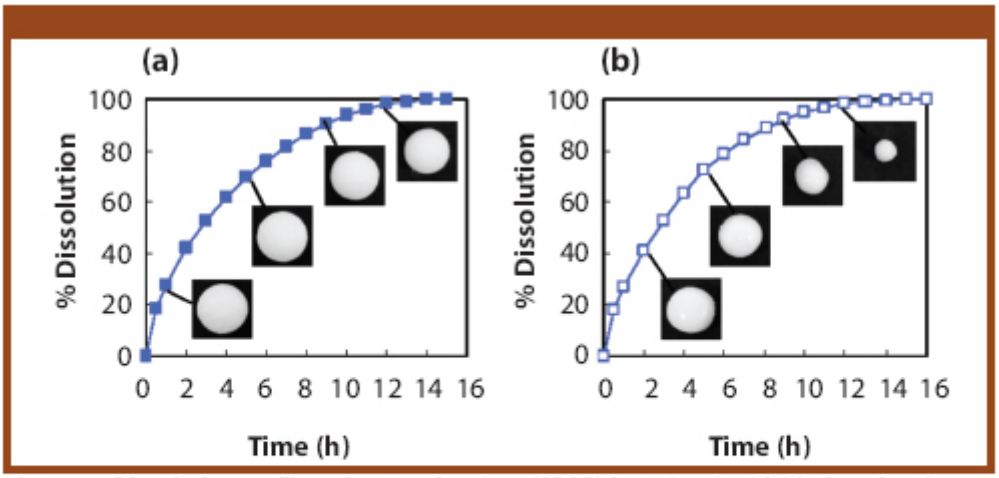

Figure 4: Dissolution profiles of acetaminophen (APAP) from (a, ■) a highly functional pregelatinized starch (HS) and (b, □) hydroxypropyl methylcellulose (HPMC) matrix tablets using a USP Type 1 apparatus at 100 rpm in a JP-2 buffer containing α-amylase in a 5-μg/L concentration. The formulation of the tablets was HPMC/APAP/microcrystalline cellulose = 60%/10%/30%.

Table 1

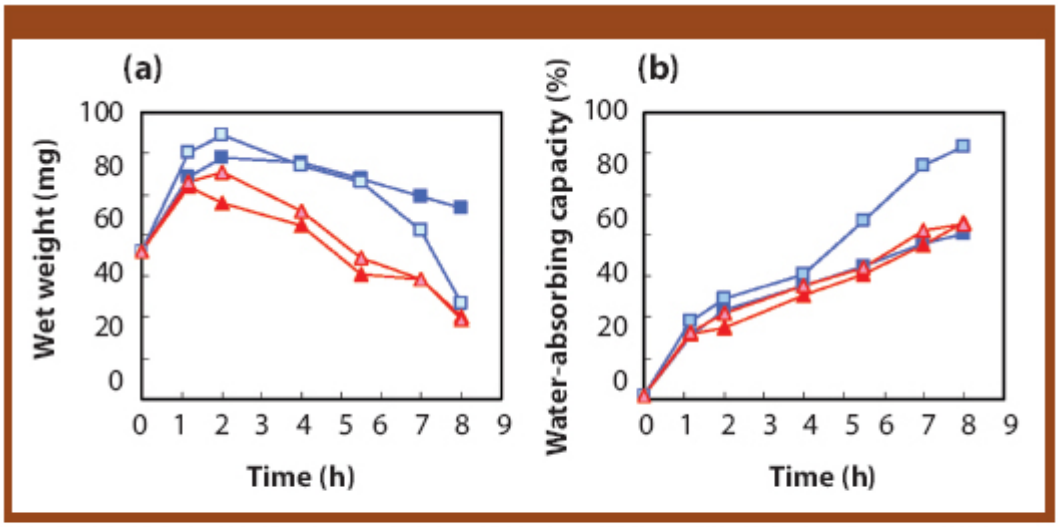

Figure 8: The change of (a) weight and (b) water-absorbing capacity of (■) a highly functional pregelatinized starch (HS) tablet without polyethylene glycol (PEG), (▣) a HS tablet with PEG, (▲) a hydroxypropyl methylcellulose (HPMC) tablet without PEG, and (△) a HPMC tablet with PEG in a dissolution test.

Figure 4

Figure

8

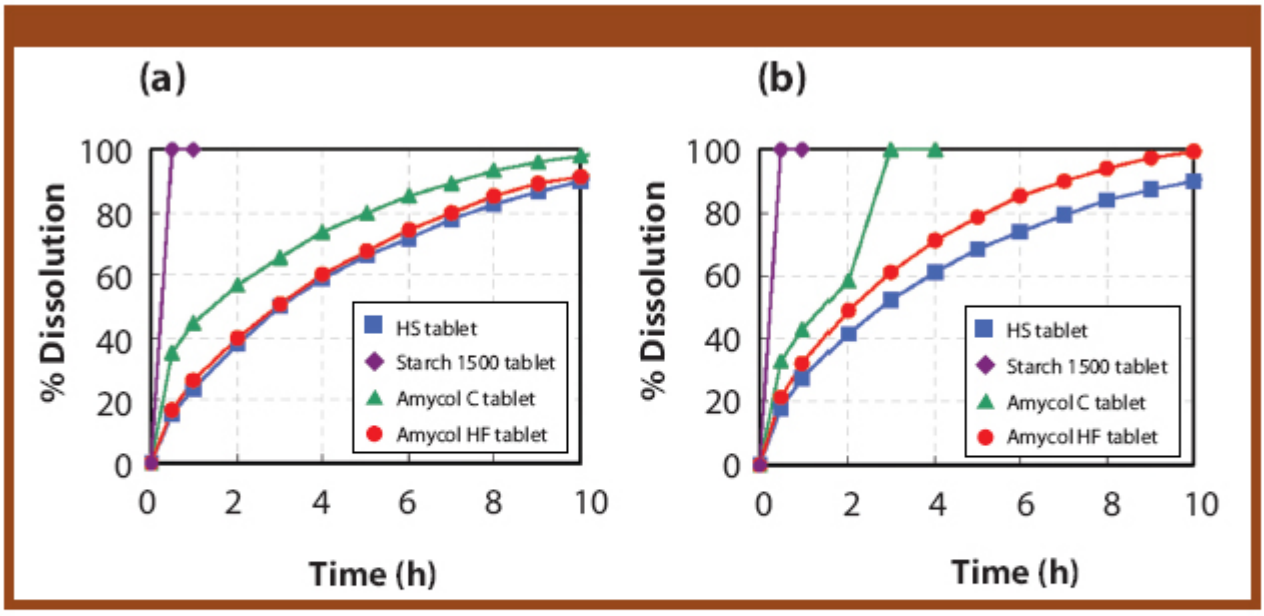

Figure 2: The influence of α-amylase on acetaminophen (APAP) release profiles from (■) a highly functional pregelatinized starch (HS) tablet, (◆) a Starch 1500 tablet, (▲) an Amycol C tablet, and (●) an Amycol HF tablet using a USP Type 1 apparatus at 100 rpm in a JP-2 buffer (a) without α-amylase or (b) with α-amylase in a 5-µg/L concentration. The formulation of the tablets was starch/APAP/microcrystalline cellulose = 60%/10%/30%.

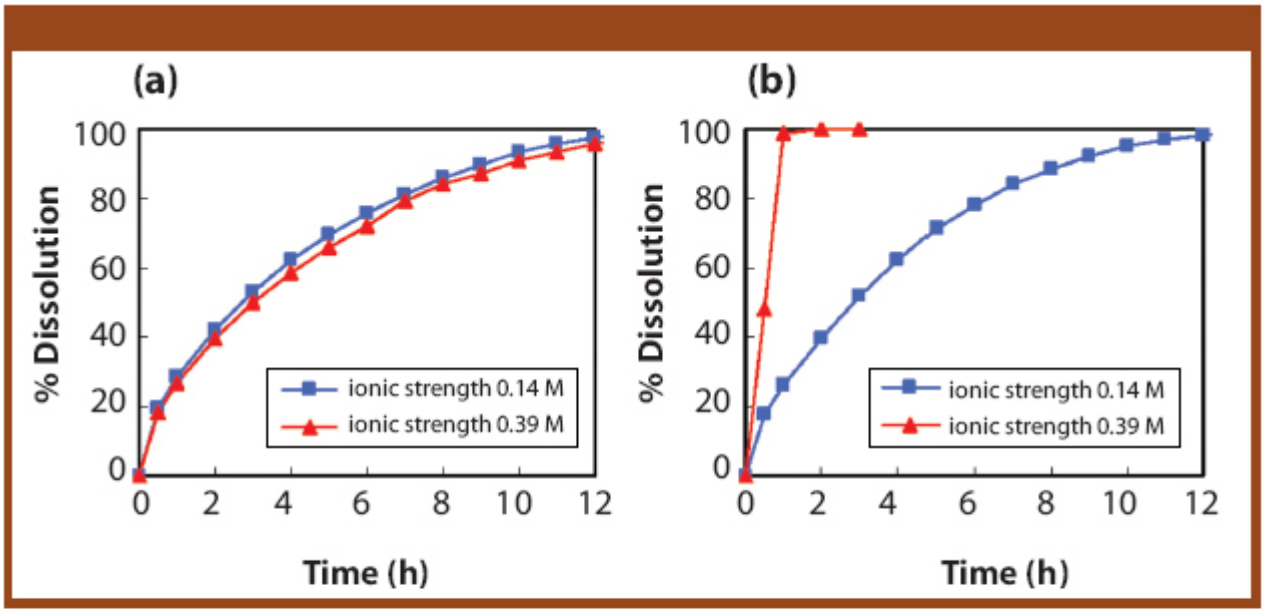

Figure 3: Dissolution profiles of acetaminophen (APAP) from (a) a highly functional pregelatinized starch (HS) and (b) hydroxypropyl methylcellulose (HPMC) matrix tablets using a USP Type 1 apparatus at 100 rpm. The test media was a JP-2 buffer with α-amylase in a 5-µg/L concentration and McIlvain buffer with α-amylase in a 5-µg/L concentration. The formulation of the tablets was HS or HPMC/APAP/microcrystalline cellulose = 60%/10%/30%.

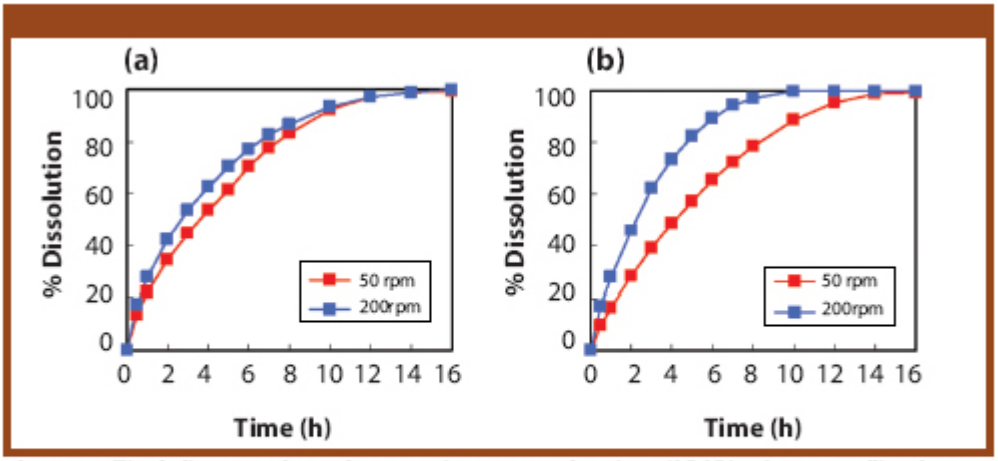

Figure 5: The influence of rotation speed on acetaminophen (APAP) release profiles from (a) a highly functional pregelatinized starch (HS) and (b) hydroxypropyl methylcellulose (HPMC) matrix tablets using a USP Type 2 apparatus in JP-2 buffers containing α-amylase in a 5-µg/L concentration at rotation speed of (■) 50 rpm and (■) 200 rpm. The formulation of the tablets was HS or HPMC/APAP/microcrystalline cellulose = 60%/10%/30%.

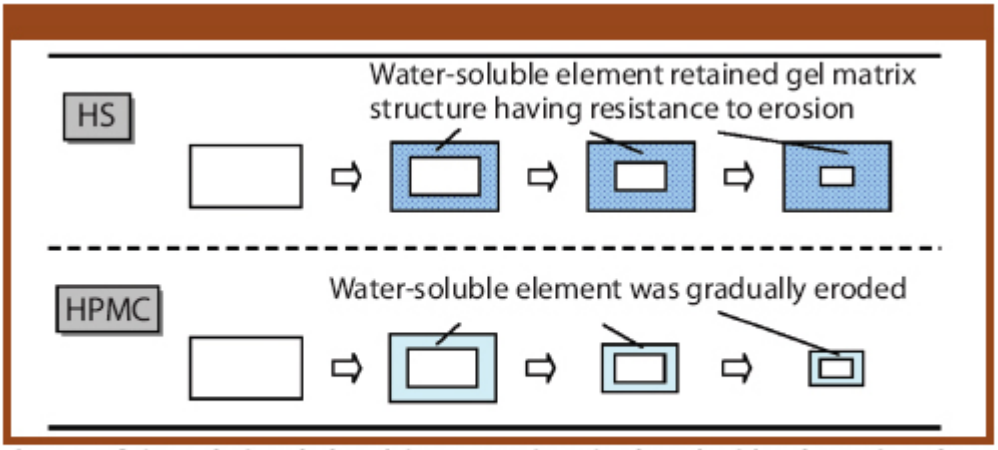

Figure 6: Schematic description of the assumed mechanism of gel forming and erosion

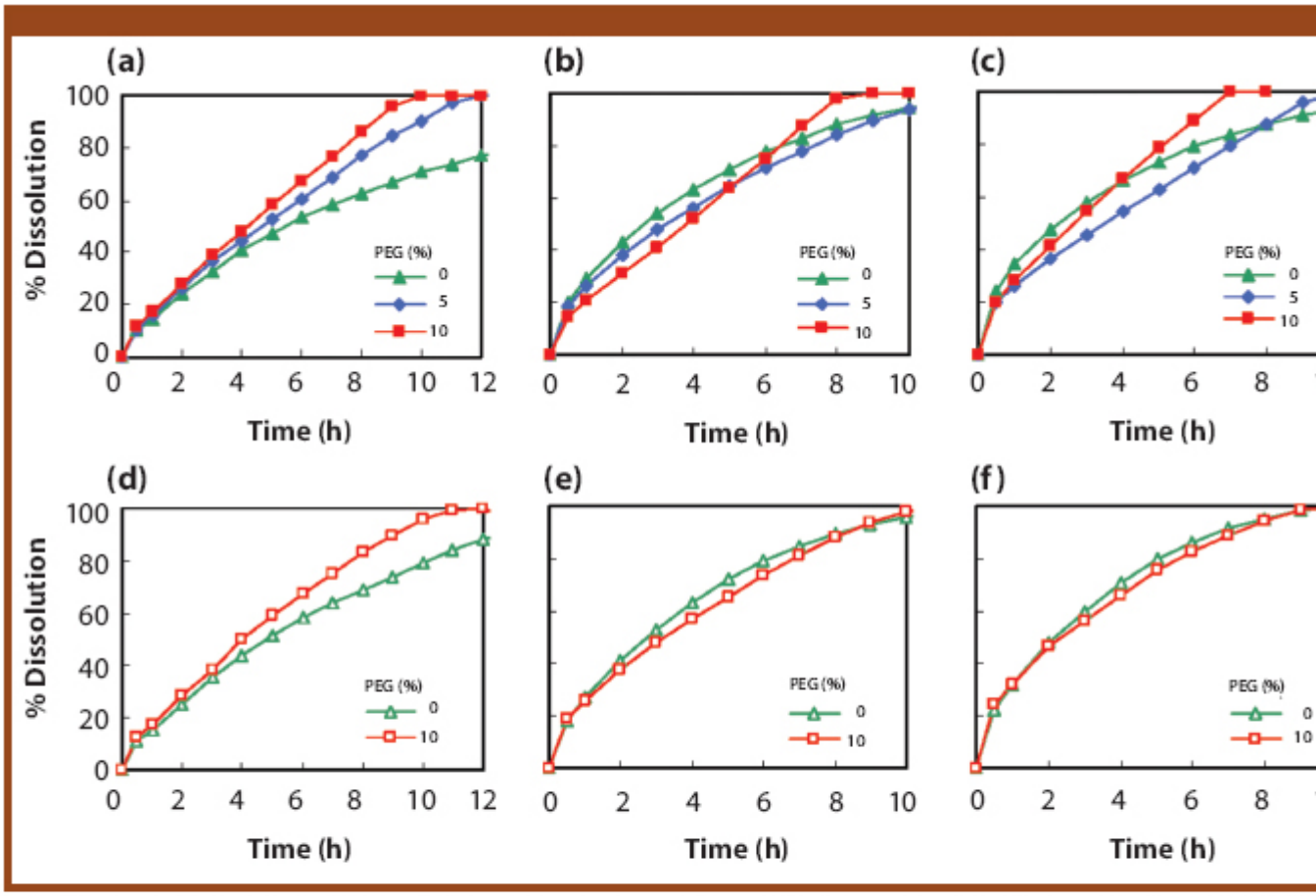

Figure 7: The influence of polyethylene glycol (PEG) on drug-release profiles from a highly functional pregelatinized starch (HS) and hydrox
methylcellulose (HPMC)

Table II: The formulations of tablets.

	Components	Tablet a	Tablet b	Tablet c	Tablet d	Tablet e	Tablet f
Matrix excipient	HS	60%	60%	60%	-	-	-
	HPMC	-	-	-	60%	60%	60%
Model drug	ETZ	10%	-	-	10%	-	-
	APAP	-	10%	-	-	10%	-
	SSA	-	-	10%	-	-	10%
Other excipients	MCC	10–20%	20–30%	20–30%	20–30%	20-30%	15–30%
	Sorbitol	10%	-	-	-	-	-
	PEG	0–10%	0–10%	0–10%	0–10%	0–10%	0–15%

HS is a highly functionalized pregelatinized starch. HPMC is hydroxypropyl methylcellulose. ETZ is ethenzamide. APAP is acetaminophen. SSA is sodium salicylic acid. MCC is microcrystalline cellulose. PEG is polyethylene glycol.

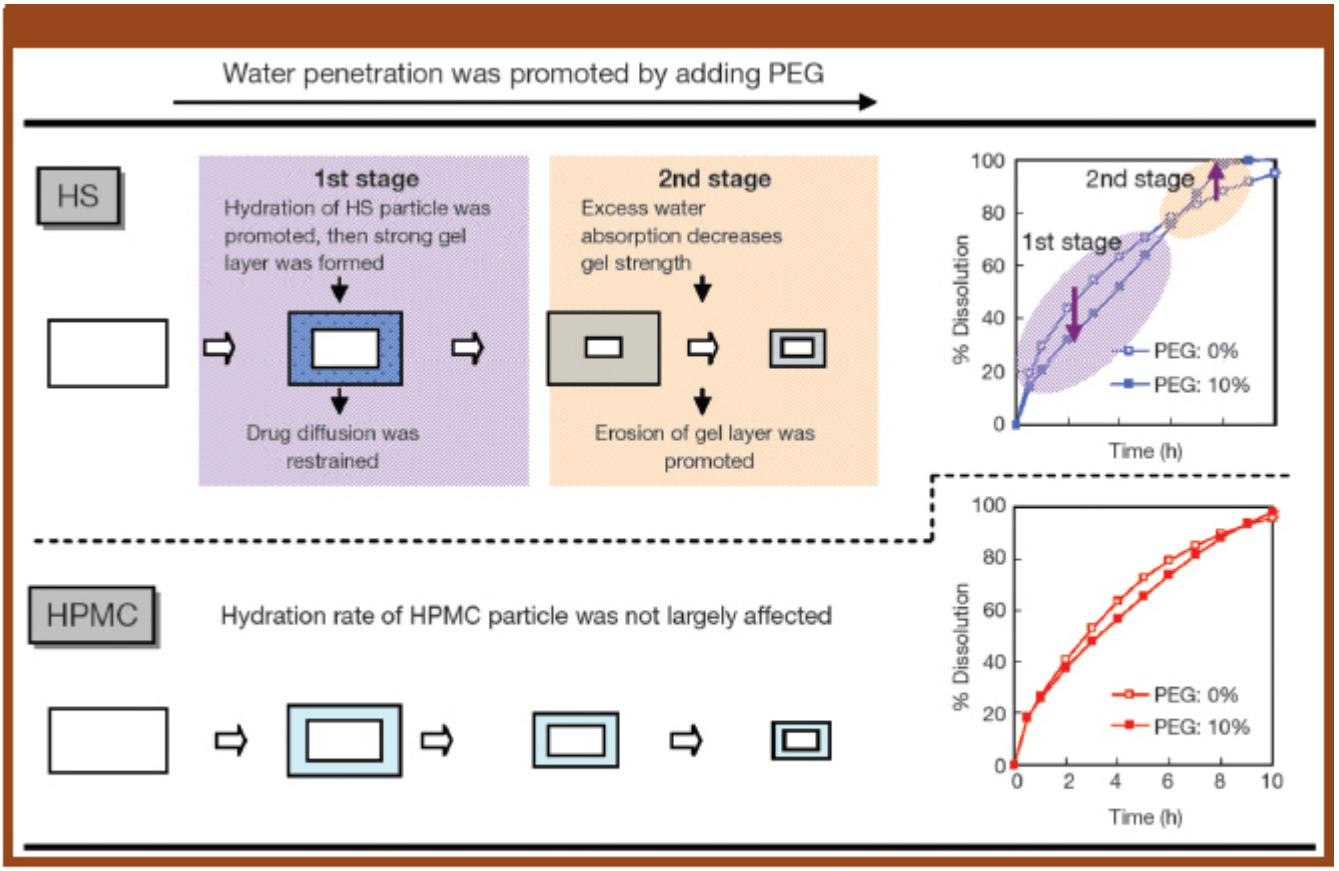

Figure 9: Schematic description of assumed mechanism of different actions between a highly functional pregelantized starch (HS) and hydroxypropyl methylcellulose (HPMC) matrix tablet caused by promotion of water penetration into tablets by adding polyethylene glycol (PEG).

Table III: The formulations of tablets.

	Components	Tablet a	Tablet b	Tablet c	Tablet d
Matrix excipient	HS	60%	60%	-	-
	HPMC	-	-	60%	60%
Model drug	APAP	10%	10%	10%	10%
Other excipients	MCC	30%	20%	30%	20%
	PEG	-	10%	-	10%

HS is a highly functionalized pregelatinized starch HPMC is hydroxypropyl methylcellulose. APAP is acetaminophen. MCC is microcrystalline cellulose. PEG is polyethylene glycol.

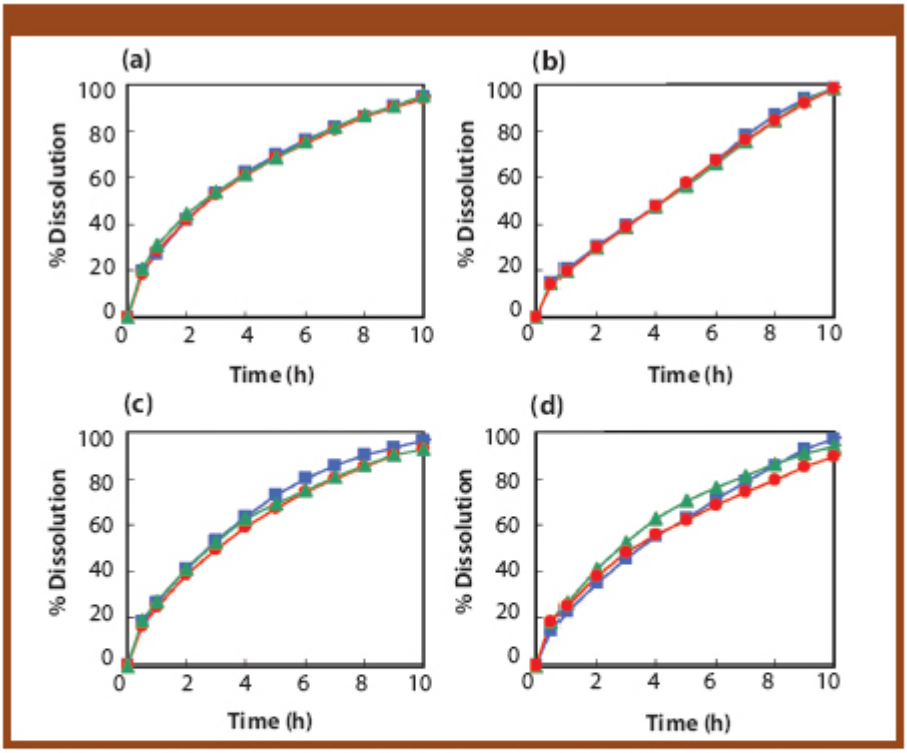

Figure 10: The dissolution profiles of acetaminophen (APAP) from a highly functional pregelatinized starch (HS) and hydroxypropyl methylcellulose (HPMC) tablets with or without polyethylene glycol (PEG) using a USP Type 1 apparatus at 100 rpm in a JP-2 buffer containing α-amylase in a 5-µg/L concentration. The symbols express storage conditions: (■) initial, (▲) 40 °C and 75% relative humidity (RH) for 6 months, and (●) 60 °C for 6 months. The formulations of the tablets were (a) HS/APAP/microcrystalline cellulose (MCC) = 60%/10%/30%, (b) HS/APAP/MCC/PEG = 60%/10%/20%/10%, (c) HPMC/APAP/MCC = 60%/10%/30%, and (d) HPMC/APAP/MCC/PEG = 60%/10%/20%/10%.

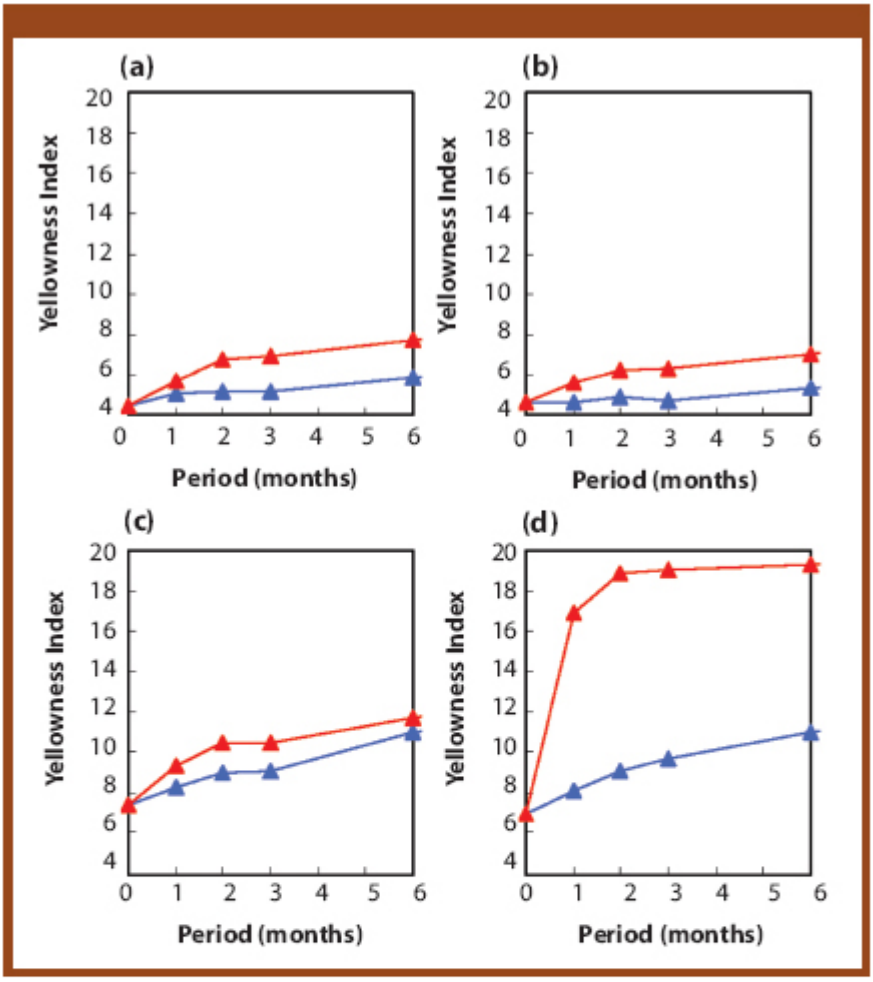

Figure 11: The yellowness index of a highly functional pregelatinized starch (HS) and hydroxypropyl methylcellulose (HPMC) tablets with or without polyethylene glycol (PEG). The symbols express storage conditions: (▲) 40 °C and 75% relative humidity, and (▲) 60 °C. The formulations of the tablets were a) HS/APAP/microcrystalline cellulose (MCC) = 60%/10%/30%, (b) HS/APAP/MCC/PEG = 60%/10%/20%/10%, (c) HPMC/APAP/MCC = 60%/10%/30%, and (d) HPMC/APAP/MCC/PEG = 60%/10%/20%/10%.

Figure 2

Figure 3

Figure 5

Figure 6

Figure 7

Table 2

Figure 9

Table 3

Figure 11

Figure 12