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Sustained Release Characteristics of Tablets Prepared with Mixed Matrix of Sodium Carrageenan and Chitosan: Effect of Polymer Weight Ratio, Dissolution Medium, and Drug Type

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ABSTRACT The interpolymeric complexation of carrageenan and chitosan was investigated for its effect on drug release from polymeric matrices in comparison to single polymers. For this purpose, matrices with carrageenan: chitosan (CG:CS) ratios of 100%, 75%, 50%, 25%, and 0% were prepared at 1:1 drug to polymer ratio. The effect of dissolution medium and drug type on drug release from the formulations was addressed. Two model drugs were utilized: diltiazem HCl (DZ) as a salt of a basic drug and diclofenac Na (DS) as a salt of an acidic drug. Three dissolution media were used: water, simulated gastric fluid (SGF), and simulated intestinal fluid (SIF). Some combinations of the two polymers showed remarkable sustained release effect on DZ in comparison to the single polymers in water and SGF. However, no apparent effect for the combination on DZ release was shown in SIF. The medium effect was explained by the necessity of chitosan ionization, which could be attained by the acidic SGF or microacidic environment created by the used acidic salt of DZ in water, but not in SIF. An interaction between the medium type and CG:CS ratio was also found. With DS, the polymer combinations had similar dissolution profiles to those of the single polymers in water and SIF, which was explained by the lack of chitosan ionization by the medium or the drug basic salt. The dissolution profiles could not be obtained in SGF, which was attributed to the conversion of DS into diclofenac free acid. The importance of chitosan ionization for its interaction with CG to have an effect on the release of DS was demonstrated by performing dissolution of SGF presoaked tablets of DS in SIF, which showed an effect of combining the two polymers on sustaining the drug release.

KEYWORDS Carrageenan, Chitosan, Interpolymeric complexation, Sustained release matrices, Diltiazem HCl, Diclofenac Na

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INTRODUCTION

The ionic interaction between oppositely charged polymers, such as polyelectrolyte complexation of sodium alginate and chitosan or poly(acrylic acid) and chitosan, has been exploited for sustained drug release (Oda et al., 1995; Tapia et al., 2002; Torre et al., 2003). In a study for oral mucoadhesive tablets of chitosan and sodium alginate, in vitro release of diltiazem could be modified by changing the mixing ratio of chitosan and sodium alginate, increasing chitosan content in the tablets and/or viscosity grade of the alginate (Oda et al., 1995). In another similar study, the release of diltiazem from tablets based on mixtures of chitosan/alginate was dependent on the pH of the dissolution media, degree of polymerization of chitosan, and the quantity of chitosan in the formulation (Tapia et al., 2002). The noncovalent polyionic complexation between polyacrylic acid and chitosan was investigated for localized antibiotic delivery in the stomach and it was found that freeze-dried interpolymeric complex could serve as a potential candidate for amoxicillin delivery in an acidic environment (Torre et al., 2003).

Chitosan is a linear aminopolysaccharide of β-D glucosamine units joined by (Oda et al., 1995; Tapia et al., 2002; Torre et al., 2003; Winterowd & Sanford, 1995) β glycosidic linkages (Winterowd & Sanford, 1995). Chitosan acquires a positive charge when exposed to acid/water mixtures because of the protonation of primary amino group, and as a result it coagulates if negatively charged molecule is added to the solution (Winterowd & Sanford, 1995). Carrageenans are naturally occurring anionic polysaccharides extracted from red seaweed (Gupta et al., 2001). They consist of the sulfate esters of galactose and 3,6-anhydrogalactose copolymers (Picker, 1999). Polyelectrolyte complex of carrageenan and chitosan has been previously prepared by mixing chitosan and κ-carrageenan solutions (Sakiyama et al., 1993). The disappearance of electrostatic linkage between the amino group of chitosan and the sulfonate group of carrageenan in the prepared complex was found to contribute to the swelling of the complex gel. Fourier-transform infrared (FTIR) analysis for the complexation of chitosan and carrageenan evidenced the formation of strong polyelectrolyte complex and the involvement of $-NH_3$ groups of chitosan and the $-SO_4$ groups of carrageenan (Tapia et al., 2004). The polyelectrolyte complex of κ-carrageenan and chitosan was utilized for the coating of controlled-release theophylline capsules (Tomida et al., 1994). The theophylline release from the coated capsule followed zero-order kinetics, and the release rates were independent of pH of the dissolution medium.

The use of interpolymeric complexation for the purpose of sustained drug release was mainly studied for alginate-chitosan system particularly by microencapsulation, while the use of carrageenan-chitosan system is not routinely addressed in the literature. The importance of using carrageenan instead of alginate is the difference in the acidic moiety between the two polymers. The sulfonate group in carrageenan is strongly acidic, which allows for ionization even at low pH values. On the other hand, alginate has a weakly acidic carboxylate group that cannot maintain ionization at low pH values. In this study the objective was to evaluate the effect of combining carrageenan and chitosan in a matrix on drug release in comparison to the use of each single polymer. Because the interaction between the two polymers is anionic, this interaction could be affected by the ratio of the two polymers, pH of the dissolution medium, and the ionic nature of the dispersed drug upon dissolution. The effect of drug type and dissolution medium is not addressed in the literature for matrices of combined carrageenan and chitosan. Accordingly, we studied the effect of carrageenan:chitosan ratio, dissolution media, and drug type on drug release from matrices of combined carrageenan and chitosan. Three dissolution media were used: water, simulated intestinal fluid (pH 7.4), and simulated gastric fluid (pH 1). Two model drugs were selected: diltiazem HCl as a salt of a basic drug and diclofenac Na as a salt of an acidic drug.

MATERIALS AND METHODS

Materials

Chitosan (CS) from the Jordanian Pharmaceutical Company, Naur, Jordan, has a degree of deacetylation of 91.2% and viscometric molecular weight of 1% solution of 38 mPas. second, which was determined at 25°C using a Brookfield viscometer at spindle number 3, and shear rate 60 rpm. Multiple type Na carrageenan (CG) was from BDH Chemicals (Poole, England). Diltiazem HCl (DZ) was from DAR Al-DAWA Pharmaceutical Company (Naur, Jordan).

Diclofenac sodium (DS) was from Al-Hikma Pharmaceutical Company (Amman, Jordan).

Evaluation of Interpolymeric Complex

An aqueous solution of 0.4% CG was mixed with an equal volume of 0.4% CS solution in 0.1 M HCl. The mixture was incubated at 37°C for 24 h, and then centrifuged at 15,000 rpm for 15 min. The obtained coprecipitate was washed with distilled water, dried under vacuum at room temperature for 24 h, and then milled using mortar and pestle. The product was analyzed by differential scanning calorimetry (DSC) at 10°C/min scanning rate (Mettler TA4000) in comparison to CG and CS. The samples were subjected to heating from 50° to 100°C with subsequent cooling to room temperature in order to remove free moisture, and then scanned from 50° to 250°C.

Formulation and Preparation of the Tablets

Drug (DZ or DS) was mixed manually using a mortar and pestle with CG and/or CS in various ratios. The ratios of CG:CS for the polymer combinations were 75%, 50%, and 25% and the drug:polymer ratio in the mixtures was 1:1. The mixtures were granulated with absolute ethanol using mortar and pestle. The granulations were dried in an oven at 40°C, passed through a 16-mesh sieve, and then mixed with 1% magnesium stearate using mortar and pestle. From each lubricated granulation, a powder quantity equivalent to 120 mg DZ or 100 mg DS was compressed into a tablet in 1 cm die using manual tableting hydraulic press. The compression force for tableting was adjusted to give tablet hardness values of 10 ± 1 Kp.

Dissolution Studies

The dissolution studies were performed in triplicate using type II dissolution apparatus (paddle method) in 900 mL dissolution medium at 37°C and 75 rpm. The dissolution media used were distilled water, enzyme free simulated gastric fluid (SGF), and enzyme free simulated intestinal fluid (SIF). At 1-h sampling intervals, 5 mL were drawn from the dissolution medium and analyzed for % drug release using UV spectrophotometer (Ultrospec II spectrophotometer) at wavelength of 237 nm for DZ and 275 nm for DS. The samples were not replaced with the dissolution medium, which was corrected for in the calculation of % drug release. No interference due to the dissolved CS or CG was evident at these wavelengths. The dissolution data were fitted according to power law (Ritger & Peppas, 1987):

$$M_t/M_\infty = kt^n$$

where M_t/M_∞ is the fraction of drug released in time t, k is the apparent release rate constant, and n is the diffusional exponent. The fitting was performed for $Mt/M_\infty \leq 0.6$ by linear regression of log (Mt/M_∞) vs. log time at level of significance of 0.05.

RESULTS AND DISCUSSION

DSC scans of CG, CS, and the complex are reported in Fig. 1. CG showed a sharp exothermic peak at 225°C, which was related to oxidative degradation. Chitosan had no distinctive peaks within the studied temperature range. On the other hand, the DSC of the coprecipitate showed the disappearance of the exothermic peak of CG and the appearance of a new broad exothermic peak at 201°C, which might indicate change in the thermal stability of CG as a result of complexation.

The dissolution profiles of DZ in the three studied dissolution media are shown in Figs. 2a, 2b, and 2c. Except for CG:CS ratio of 25% in SGF, the combinations had slower drug dissolution rates than

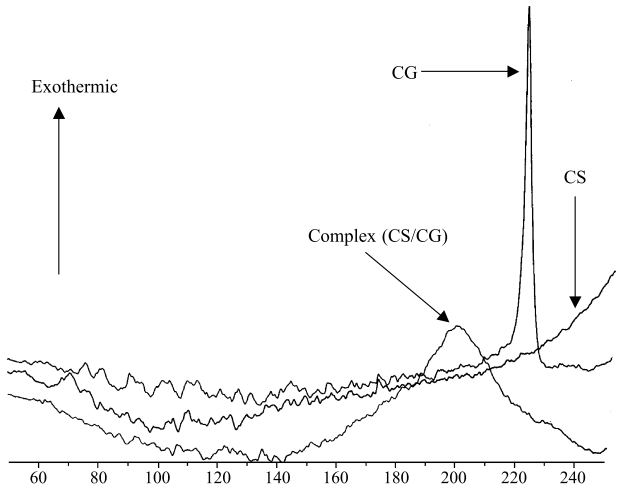

FIGURE 1 DSC of CS, CG, and the Complex CS/CG.

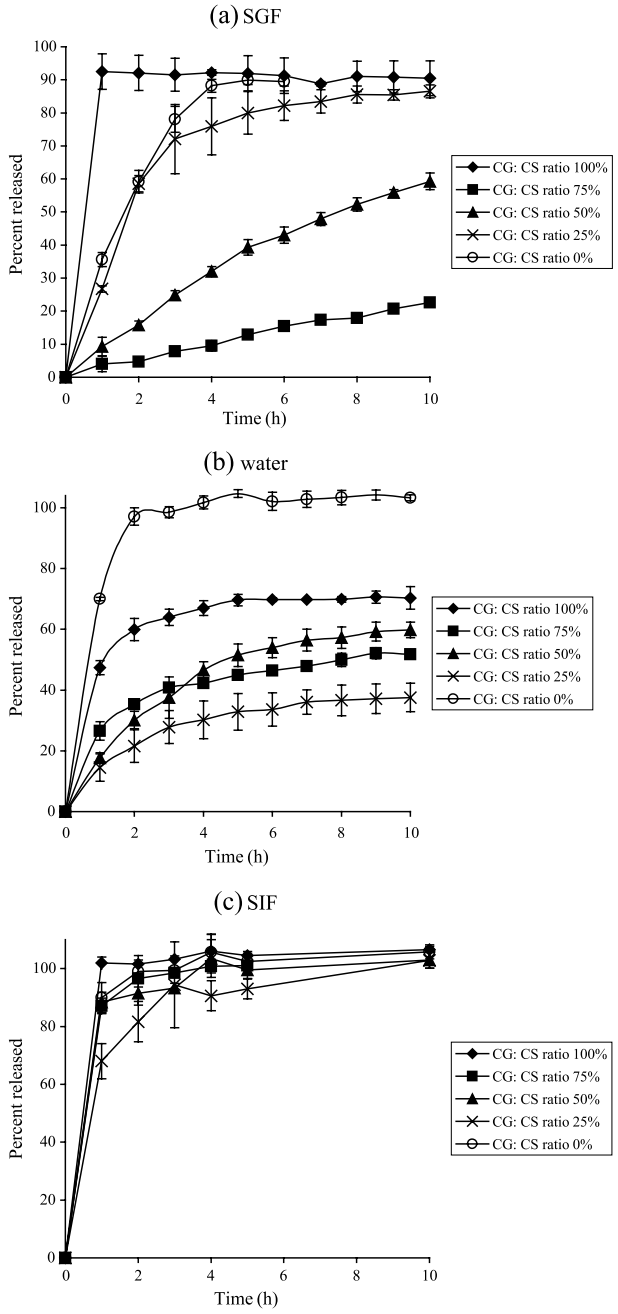

FIGURE 2 **Dissolution Profiles of DZ in Various Media from Tablets Containing CG and/or CS in Various Ratios. (a) SGF. (b) Water. (c) SIF. Each Plotted Value is the Mean of n=3 and SD is Shown as Error Bar.**

the single polymers in SGF and water. In contrast, the combinations had similar dissolution profiles to those of the single polymers in SIF. These results indicate significant interaction between the two polymers in water and SGF, but not in SIF. Carrageenan molecule has strong acidic sulfate groups that allow a certain degree of ionization to be maintained even at low pH (Bonferoni et al., 1994; Graham et al., 1963), however, the ionization of the amino group of chitosan (pK_a 6.3) decreases greatly when the solution pH increases above 6.0 (Yalpani & Hall, 1984). Accordingly, the ionization of chitosan could be a limiting factor for its interaction with carrageenan. The insignificant ionization of chitosan in the high pH SIF, and the significant ionization of chitosan by the acidic SGF or the microacidic environment created by the acidic salt of diltiazem in water could explain the medium effect on drug release. It can be seen from the figures that the use of 100% CG or 100% CS resulted in the release of more than 50% of the drug in 2 h in all media. The % drug release from the 100% CS formulation at 2 h was 97%, and 59% in water, and SGF, respectively. On the other hand and with the 100% CG formulation, 60%, and 93% drug release at 2 h was obtained in water, and SGF, respectively. Except for CG:CS ratio of 25% in SGF, this initial burst effect in drug release obtained by using 100% CS or 100% CG was minimized or even prevented by combining the two polymers, which can be attributed to the interaction between the two polymers. This effect was illustrated for 75% and 50% CG in SGF with 2 h drug release of 5% and 16%, respectively, and for 25% CG in water with 2 h drug release of 22%. In SIF, there was a slight effect for the combination on this first burst release mostly represented by almost 100% drug release at 2 h for the single polymers and 81% drug release at 2 h for 25% CG. Some combinations of the two polymers have given rise to a remarkable sustained release of DZ in water and SGF. Almost 20% and 60% of drug were released in SGF in 10 h in almost zero order using 75% and 50% CG, respectively. In water, the combinations showed between 25% and 60% drug release in 10 h. However, the release of DZ in water from the combinations was leveled off after 5 h, indicating the release was not controlled. In a recent study, the possibility of using mixtures and/or polyelectrolyte complexes from chitosan-carrageenan type I as prolonged diltiazem clorhydrate release systems and the swelling behavior of these systems were evaluated (Tapia et al., 2004). The swelling behavior studies done for tablets at various ratios of the two polymers with no other additives in 0.1 N HCl showed higher swelling for the chitosan-carrageenan systems than for the single polymers, which is in agreement with the dissolution results in our study

TABLE 1 Effect of CG:CS Ratio on the Initial Burst Effect and Power Law Parameters (Apparent Release Rate Constant k and Diffusional Exponent n) of DZ in Various Media

CG:CS ratio	Drug release at 2 h (%)			k^a (h^{-1})		n^a	
	Water	SGF	SIF	Water	SGF	Water	SGF
100%	59.9±(3.6)	92.1±(5.3)	101.9±(7.4)	–	–	–	
75%	35.4±(0.8)	4.7±(1.2)	96.6±(1.7)	0.2890± (0.0096)	0.0333± (0.0096)	0.2703± (0.0077)	0.8630± (0.2106)
50%	30.1±(2.9)	15.8±(1.2)	91.5±(4.1)	0.1952± (0.0161)	0.0948± (0.0164)	0.5589± (0.0021)	0.8403± (0.0739)
25%	21.5±(5.4)	58.6±(2.4)	81.6±(81.6)	0.1612± (0.4038)	–	0.4165± (0.0793)	–
0%	97.1±(2.9)	59.2±(3.4)	99.0±(5.4)	–	–	–	–

Each value represents the mean of three determinations and SD is given in parenthesis.
[a]Was not given for SIF because % dissolved at 3 h was more than 60% for all formulations.

when considering that the swelling behavior of the polymers controls the drug release from a matrix. However, the dissolution studies for DZ formulations based on these systems appeared low retardant capacity of drug release of these systems compared to the single polymers, which is not consistent with the dissolution results of our study. These dissolution studies were performed for tablets with only 20% w/w of chitosan-carrageenan and 61% lactose and the tablets were prepared by direct compression, while in our study no diluent was used, the total polymer concentration in the tablets was 50%, and the tablets were prepared by wet granulation using ethanol. Accordingly, the differences in formulation and tablet preparation between the two studies could explain the found inconsistency. In order to evaluate the effect of CG:CS ratio and dissolution medium on sustaining the release of DZ, two parameters were obtained and listed in Table 1: the % drug release at 2 hr, which was taken to account for the initial burst effect, and the apparent release rate constant obtained from power law. Formulations with % drug release more than 60% at 3 h were not fitted to power law because of leaving only two points for regression, and thus they were not considered as sustained release formulations. Based on this criteria, all the sustained release formulations were combinations of the two polymers, indicating the inability of each polymer alone to sustain the drug release, which can be attributed to high drug:polymer ratio and high water solubility of DZ, and the high efficiency of combining the two polymers in sustaining the drug release. Table 1 shows that the effects of combining the two polymers on preventing the burst effect and on the apparent release rate were dependent on CG:CS ratio, and this dependence varied according to the dissolution medium. It is seen from Table 1 that the burst effect in water was the greatest for CG:CS ratio 0%, i.e., when the formulation did not contain carrageenan. This is in accordance with Fig. 2b. However, with formulations containing carrageenan decrease in CG:CS ratio (CG:CS ratio decreased from 100% to 25%) resulted in suppressed burst effect and decrease in release rate in water. The opposite was obtained in SGF, as these two parameters tended to increase with the decrease in CG:CS ratio. Accordingly, higher CS amount with respect to CG was needed for more slow down of DZ release in water than in SGF. The greater expected ionization of CS by HCl in SGF than by the drug microacidic environment in water could explain the interaction effect between CG:CS ratio and dissolution medium type on drug release.

The dissolution profiles of DS for the matrices with various CG:CS ratios in water and SIF are shown in Figs. 3a and 3b, respectively. The drug dissolution profiles in SGF are not shown because insignificant UV absorbance values were obtained for the SGF samples (<0.05), and this was attributed to the conversion of DS into diclofenac free acid, which is practically insoluble in the acidic SGF. Similar to DZ, there are slight differences in DS release in SIF between the formulations; the combinations of the two polymers had similar dissolution rates, which were slightly slower than that of 100% CS and slightly higher than that of 100% CG. In contrast to the results obtained with DZ in water, no apparent differences in

DS release in water can be seen between the 100% CG or 100% CS formulation and the combinations of the two polymers. This is consistent with the proposed ionization of chitosan by the microacidic environment created by DZ by considering the basic nature of DS that would not lead to such environment, and consequently, would lead to insignificant chitosan ionization for the interaction of the two polymers. In order to have a more sound conclusion for the necessity of CS ionization for CS-CG interaction, tablets of each DS formulation were subjected to dissolution for 2 h in SGF, in which CS can be highly ionized by the acidic medium and interacts with CG. The same gastric soaked tablets were filtered from the dissolution medium and exposed to further drug dissolution in SIF for an additional 8 hrs. After the exposure to SGF and in SIF, the polymer combinations have given rise to a delay in drug release and clearly lower drug release rates than each polymer alone (Fig. 4), which supports the hypothesis of the CS ionization as a limiting factor for its interaction with CG. It is unlikely that the delay in drug was due to DS, such as the slow ionization of diclofenac free acid

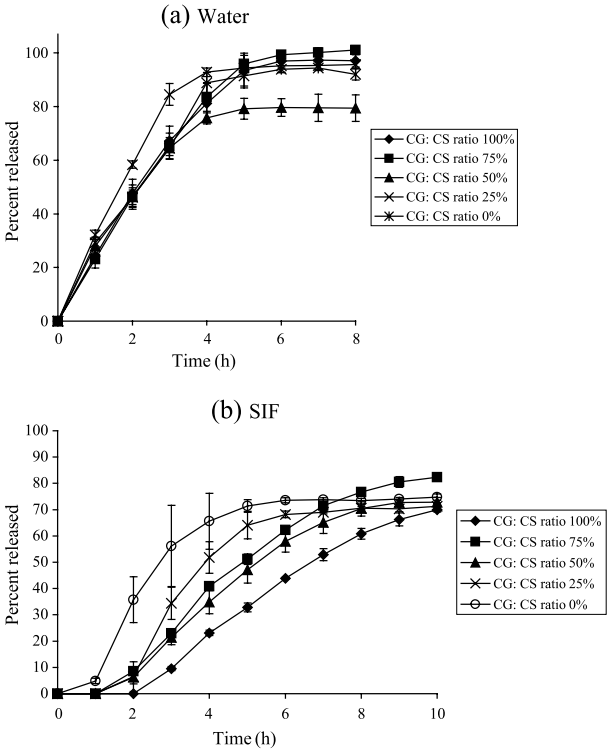

FIGURE 3 **Dissolution Profiles of DS in Water and SIF from Tablets Containing CG and/or CS in Various Ratios. (a) Water. (b) SIF. Each Plotted Value is the Mean of n=3 and SD is Shown as Error Bar.**

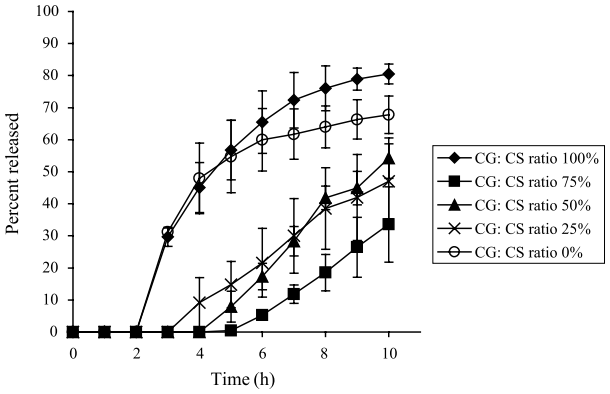

FIGURE 4 **Dissolution Profiles of DS in SIF After Gastric Presoak From Tablets Containing CG and/or CS in Various Ratios. Each Plotted Value is the Mean of n=3 and SD is Shown as Error Bar.**

formed in the SGF, because no delay was obtained for the 100% CS and the 100% CG formulations. Accordingly, the delay in drug release could be attributed to the complex formation between the two polymers in SGF before the exposure to SIF. This delay was for 1, 2, and 3 h for 25%, 50%, and 75% CG:CS ratio, respectively. In addition, the calculated apparent release rate constants were 0.0869, 0.0814, and 0.0529 for 25%, 50%, and 75% CG:CS ratio, respectively. These results indicate higher complexation between the two polymers in SGF in the presence of DS with the increase in CG:CS ratio and are consistent with that obtained for effect of CG:CS ratio on the prevention of the initial burst effect and sustained release rate of DZ in SGF.

CONCLUSIONS

The efficiency of combining CS and CG in prolonging drug release from tablet matrices in comparison to the single polymers appeared to be limited by the ionization of CS to significantly interact with strong acidic CG. This limiting factor seemed to be affected by the drug type and/or the dissolution medium. The combination was effective in sustaining the release of DZ in SGF and water, which was attributed to significant chitosan ionization that could be achieved by the acidic SGF or the microacidic environment, which could be created by the acidic salt of diltiazem in water. However, combing the two polymers was not effective in sustaining the release of DZ in SIF, and the release of DS in SIF or

water. Consequently, insignificant interaction could be concluded in the high pH SIF regardless the drug type, and in water in the presence of DS due to the basic nature of the drug salt. The effect of the interaction of the two polymers in the acidic SGF on the release of DS could not be directly revealed due to the poor solubility of DS in the medium, but was ascertained by performing dissolution on SGF pre-soaked DS tablets with various CG:CS ratios in SIF.

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