

## Influence of ionic strength on matrix integrity and drug release from hydroxypropyl cellulose compacts

J.L. Johnson <sup>a</sup>, J. Holinej <sup>b</sup> and M.D. Williams <sup>c</sup>

<sup>a</sup> Aqualon Pharmaceutical Laboratory, Aqualon Company, Wilmington, DE 9808-1599 (USA), <sup>b</sup> Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Co., Morris Plains, NJ 07950 (USA) and <sup>c</sup> Philadelphia College of Osteopathic Medicine, Philadelphia, PA 19101 (USA)

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### Summary

Hydroxypropyl cellulose (HPC) is commonly used in formulating hydrophilic sustained release matrix tablets. Since ions can affect the degree of hydration and solution viscosity of HPC, there was concern whether these ionic changes will affect the drug release rate of tablets containing HPC. The objective of this study was to determine the effect of ionic strength solutions on the matrix integrity and drug release from HPC sustained release matrix compacts. In addition, the influence of HPC particle size and molecular weight on this system was investigated. Pure HPC and drug/HPC compacts were manufactured on an instrumented tablet press and tested for disintegration and dissolution under various ionic strength NaCl solutions. At ionic strengths less than 0.5, the compacts underwent swelling and gelation without any disruption of the matrix integrity or increased drug release. At 0.5-1.0 ionic strengths, certain types of HPC disaggregated and released drug rapidly. Above 1.0 ionic strengths, the compacts did not disaggregate, although release rates remained high for the high molecular weight HPCs. Fine particle size HPC was more resistant to the influences of ionic strength changes as was lower molecular weight HPC. The results of this study indicate that at normal physiological ionic strengths HPC compacts remain intact and release drug slowly.

### Introduction

In general, as the concentration of ions in a polymer solution increases, polymer solubility decreases. The amount of water available to hydrate the polymer is reduced because more water is

required to keep the ions in solution. The types of ions in solution affect polymer hydration to varying degrees. Cellulose ethers follow the lyotropic series in their susceptibility to ionic effects. Changes in the hydration state of a polymer in solution are manifested primarily by changes in solution viscosity and cloud point.

The effect of ions on the degree of hydration of cellulose ethers has been previously studied (Heymann, et al., 1938; Levy and Schwarz, 1958; Klug, 1971; Marriot and John, 1973; Sarkar, 1979).

*Correspondence to:* J.L. Johnson, Aqualon Pharmaceutical Laboratory, Aqualon Company, Wilmington, DE 9808-1599, U.S.A.

Klug (1971) demonstrated these effects on HPC. All of these studies have been carried out on solutions of polymers.

Since cellulose ethers play an important role in the formulation of hydrophilic sustained release matrix tablets, several investigators have sought to examine the effects of ionic strength on matrix integrity and drug release (Lapidus and Lordi, 1968; Mitchell, et al., 1990). Lapidus and Lordi (1968) were among the first to note this effect. They demonstrated rapid release of chlorpheniramine in 0.2 M solutions of sodium and magnesium sulfates from hydroxypropyl methylcellulose (HPMC) 2208 matrices. Mitchell et al. (1990) investigated the effects of various ions and concentrations on the disintegration time and dissolution of drugs from HPMC type 2208 matrices. Mitchell et al. (1990) showed that under certain conditions premature disaggregation of the matrix could occur, resulting in the immediate release of all drug in the matrix, or classic 'drug dumping'. However, Mitchell et al. (1990) did not study the dissolution behavior of the matrix beyond the point where premature disaggregation occurred.

In a brief summary article, Fagan et al. (1989) reported the results of their work with HPC, HPMC, and hydroxyethyl cellulose (HEC). Fagan et al. (1989) stated that formulated tablets containing HPC underwent premature disaggregation at ionic strengths of  $\mu = 0.1$ . Inquiries confirmed that coarse particle size HPC was employed in the study (Fagan, personal communication, 1990).

This study was undertaken because HPC had not been thoroughly investigated by any authors in the literature. Fagan et al. (1989) carried out a very brief study with HPC that may have had a significant polymer particle size effect. By studying a wide range of ionic strengths, it is anticipated that an understanding of the mechanism of premature disaggregation may be achieved. It is the purpose of this investigation to determine the effect of varying ionic strength solutions of sodium chloride on the physical integrity of pure and binary compacts of HPC of different particle sizes and molecular weights. In addition, drug release profiles were studied.

## Materials and Methods

Five different types of HPC (Aqualon Co., Wilmington, DE) were used in this investigation. The types varied in particle size and molecular weight; Table 1 summarizes the types used.

Type A material was used as received from the manufacturer and had the coarsest particle size. Type AG was prepared by milling type A. Type AS was prepared by passing type A through a 100 mesh sieve. All three A types were from the same lot of material. Types BS and CS were prepared by passing type B and C material through a 100 mesh sieve, respectively.

Pure HPC compacts were prepared by weighing 350 mg quantities of polymer and hand feeding into 3/8 inch round tooling installed on a single punch instrumented tablet press (Manesty F3 Press, Thomas Engineering Inc., Hoffman Estates, IL). The tooling was standard concave. The upper punch was set at top dead center and the power turned on. Thus, the compacts were formed individually. The compaction force was held constant at 23 kN.

Binary compacts were prepared by blending 37.5 mg of phenylpropanolamine HCl (PPA) (H. Reisman Corp., Orange, NJ) with 312.5 mg of HPC. To blend the powders, the drug and polymer were placed in a glass jar and shaken for 2 min. The batch size was 35 g. This blend was then compacted as described above. PPA was chosen as a model drug because of its high water solubility. Sink conditions with respect to solubility were demonstrated with this drug in the highest ionic strength solution used in the study.

TABLE 1  
Types of hydroxypropyl cellulose (HPC) studied

HPC type	Method of preparation	Average particle size ( $\mu\text{m}$ )	Molecular weight (weight average)
A	standard	258	1150000
AG	ground	75	1150000
AS	sifted	85	1150000
BS	sifted	93	850000
CS	sifted	73	370000

Sodium chloride (J.T. Baker Inc., Phillipsburg, NJ) was chosen as the ionic agent because it falls in the mid range of the lyotropic series in its ability to salt out polymers (Heymann, et al., 1938; Klug, 1971). Furthermore, it is the electrolyte with the greatest concentration in gastric and intestinal fluids. The ionic strengths investigated were  $\mu = 0, 0.1, 0.5, 1.0, 1.5$ , and  $2.0$ . These were selected because they covered the broadest range of ionic effects on the polymers.

Disintegration tests were carried out on all compacts using the USP XXII apparatus with disks (Van-Kel Industries, Inc., Chatham, NJ). 900 ml of solution were maintained at  $37^\circ\text{C}$ . The test was carried out until the compacts disintegrated or until 120 min elapsed.

Six dissolution methods were developed, one for each ionic strength solution used to test the binary matrix tablets. Six methods had to be developed because the concentration of NaCl was found to affect the PPA absorbance. The drug, PPA, was assayed spectrophotometrically using the first derivative of the absorbance spectrum from 200 to 300 nm using a microprocessor based diode array UV spectrophotometer (Model 8451A, Hewlett-Packard Co., Valley Forge, PA). Each dissolution method required the subtraction of the HPC absorbance from that of PPA. The USP XXII dissolution testing Apparatus 1 (basket) was used at a speed of 100 rpm (Van-Kel Industries, Inc., Chatham, NJ). The dissolution media were degassed and maintained at  $37^\circ\text{C}$ . Samples were collected with an automated system at 1, 2, 4, 8, and 12 h (Hewlett-Packard Co., Valley Forge, PA).

The dissolution data were fitted to a modified Weibull equation (Langenbucher, 1972; Langenbucher, 1976) using nonlinear regression analysis based on the Gauss-Newton-Marquardt algorithm (Valko and Vajda, 1989). From the fitted equation the area-under-the-curve (AUC) was determined by integration using the Romberg method (Miller, 1987). The equation used to fit the dissolution data is:

$$D = D_\infty (1 - e^{-(t/T_d)^\beta})$$

where  $D$  denotes the amount of drug dissolved at

time  $t$ ,  $D_\infty$  is the amount of drug dissolved after infinite time,  $t$  corresponds to time,  $T_d$  is a time parameter representing release of 63.2% of the total dose and  $\beta$  is a shape parameter

The reason for referring to this as the modified Weibull equation is that the lag time parameter was omitted because the first sample was not obtained until the 1 h dissolution time. Therefore, an accurate determination of the lag time could not be obtained from the existing data.

When the lag time parameter was retained in the Weibull equation, the final value for this parameter after the nonlinear regression was very small, usually less than 0.0001. Regardless of whether the lag time parameter was included or omitted, the sum of squared residuals (SSR) remained the same. Therefore, the lag time parameter was omitted from the equation. Although the objective of fitting the dissolution data to the equation was to obtain a single number to quantitate each dissolution curve, simplifying the equation by using less parameters resulted in more meaningful values for the remaining three parameters.

The computations for the nonlinear regression analysis and integration were carried out on a microcomputer using a program written by the authors and compiled to increase executable speed (Microsoft QuickBasic 4.5, Microsoft Corp., Redmond, WA). Typically, the nonlinear regression and integration for a dissolution curve took less than 1 min to complete.

## Results and Discussion

The sieve analysis data for the HPC particle sizes are shown in Fig. 1. In addition to the sieve sizes shown in Fig. 1, a 60 mesh sieve was also used. However, only the HPC type A was retained at this mesh sieve with 64% retained. All the other HPC types had no material retained at the 60 mesh sieve. In general, the HPCs prepared by sifting through a 100 mesh screen were slightly more coarse than the ground HPC, type AG.

Table 2 summarizes the compact physical properties. The compaction forces were all within 1.3 kN of the targeted force of 23 kN. Among the

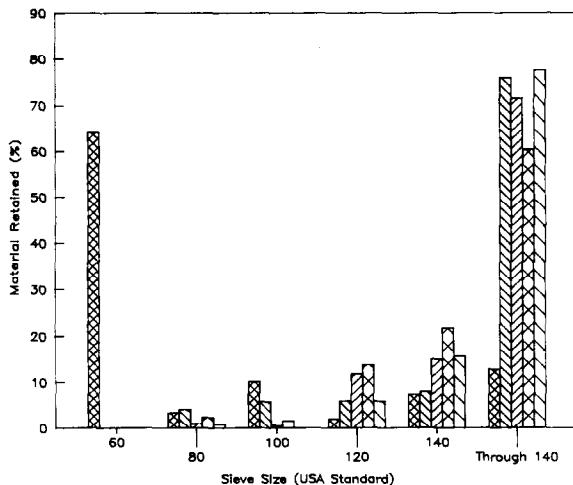


Fig. 1. Sieve analysis of HPC. (■) A HPC; (▨) AG HPC; (▨) AS HPC; (▨) BS HPC; (▨) CS HPC.

three A series of HPC compacts, the AG type yielded the hardest compacts. In comparison with the coarse particle size HPC (type A), the ground and sifted HPC binary compacts (types AG and AS) were harder. In most cases, as the particle size of the HPC was decreased, the hardness increased with a simultaneous decrease in thickness, implying that the compacts which were formed with finer particle size HPC are denser and less porous. This may be due to a greater bonding surface area associated with smaller particle size.

Table 3 lists the results of the disintegration tests. Each value represents the time at which the last of three compacts disintegrated. At  $\mu = 0$  and 0.1 no compacts disintegrated within 2 h. At these ionic strengths the compacts had a clear gel exterior and a white opaque center. The gels had the strengths necessary to resist disintegration.

As the ionic strength was increased into the  $\mu = 0.5$ –1.0 range, there were eight cases where compacts disintegrated in less than 2 h. At these ionic strengths the compacts did not form a gel, but expanded and formed somewhat spongy and friable masses with varying degrees of resistance to disintegration. Gel formation was not apparent, consequently disaggregation occurred. The polymers were most sensitive in this ionic strength range.

At  $\mu = 1.5$  and 2.0 only one compact disintegrated in less than 2 h. The non-disintegrating compacts were not significantly different from their original tablet shape and opaque appearance. They underwent only a slight change. Therefore, the polymers were essentially unreactive at these high ionic strengths.

Binary compacts had lower disintegration times (DTs) than pure compacts, indicating that the presence of drug weakened the compact. Since PPA is readily soluble, it may have increased the porosity and water penetration of the compacts. PPA also competed for the water needed to

TABLE 2  
*Summary of compact physical characteristics*

Composition of compacts	Compaction force (kN)	Hardness (kp)	Thickness (inch)	Weight (mg)
A	23.9 (0.58) <sup>a</sup>	14.4 (0.94)	0.233 (0.001)	352 (1.83)
A/PPA	23.3 (0.94)	11.0 (0.92)	0.231 (0.001)	350 (1.60)
AG	22.6 (1.20)	24.0 (0.46)	0.218 (0.001)	347 (1.77)
AG/PPA	22.3 (1.12)	20.8 (0.96)	0.217 (0.001)	349 (1.77)
AS	23.0 (0.90)	14.8 (0.65)	0.234 (0.001)	349 (1.81)
AS/PPA	23.4 (0.89)	18.4 (1.32)	0.223 (0.001)	350 (1.25)
BS	24.3 (1.27)	20.5 (0.56)	0.228 (0.001)	350 (1.89)
BS/PPA	22.3 (1.34)	19.9 (0.58)	0.224 (0.001)	349 (1.72)
CS	23.0 (1.26)	19.2 (1.30)	0.229 (0.001)	350 (1.69)
CS/PPA	22.0 (1.73)	22.6 (1.14)	0.222 (0.001)	350 (1.99)

<sup>a</sup> Values in parentheses are equal to 1 S.D.

TABLE 3

Disintegration times (in min) for HPC and HPC/PPA compacts in NaCl solutions of various ionic strengths ( $n = 3$ )

Composition of compacts	Ionic strength					
	0.0	0.1	0.5	1.0	1.5	2.0
A	> 120	> 120	49	> 120	> 120	> 120
A/PPA	> 120	> 120	23	27	105	> 120
AG	> 120	> 120	> 120	> 120	> 120	> 120
AG/PPA	> 120	> 120	> 120	40	> 120	> 120
AS	> 120	> 120	115	> 120	> 120	> 120
AS/PPA	> 120	> 120	64	> 120	> 120	> 120
BS	> 120	> 120	> 120	> 120	> 120	> 120
BS/PPA	> 120	> 120	28	118	> 120	> 120
CS	> 120	> 120	> 120	> 120	> 120	> 120
CS/PPA	> 120	> 120	> 120	> 120	> 120	> 120

hydrate the polymer. Certain compounds have the capability to elevate the cloud point of a polymer, which could increase DTs (Levy and Schwarz, 1958; Lapidus and Lordi, 1968). However, based on these results, PPA does not appear to have that capability.

A comparison of the DT values for pure and binary compacts between the high and low molecular weight HPCs (AS vs CS) shows that, as the molecular weight decreased, the DTs increased. The presence of drug had a relatively minor impact on DTs in this case. A possible reason for this is that the lower molecular weight polymer hydrates more rapidly and completely, thus offering greater protection against disaggregation.

Fig. 2 illustrates the nonlinear regression fit of the dissolution data to the modified Weibull equation. In addition to the visual confirmation of a 'goodness-of-fit' for the nonlinear regression, the SSR was monitored. Typically, the SSR values were less than unity.

Figs 3-7 show the drug dissolution curves for each of the polymers studied at the six different ionic strengths. Each curve is the average of three dissolutions. These graphs illustrate the drug release from the HPC/PPA compacts.

Dissolution results indicated that disaggregation only occurred at  $\mu = 0.5$  and 1.0 for most of the binary compacts tested. For the compacts

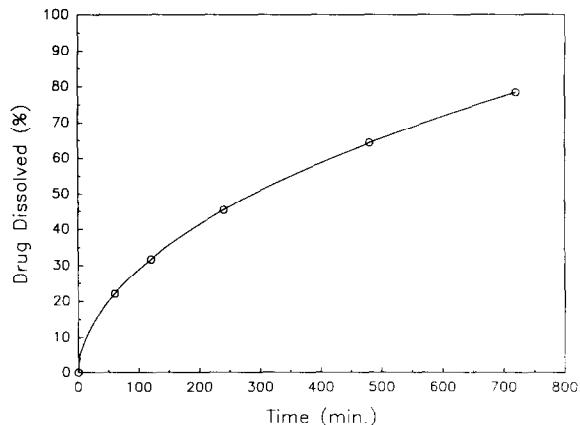


Fig. 2. Nonlinear regression fit of dissolution data to modified Weibull equation: HPC-AG/PPA compacts in  $\mu = 0.1$  NaCl solution. (○) Experimental data; (—) calculated fit to Weibull equation.

made with the A grade of HPC, dissolution was slowest at  $\mu = 0$  and 0.1 (Fig. 3). At  $\mu = 0.5$  and 1.0, the compacts released between 90 to 100% of the drug within 1 h. Finally, at  $\mu = 1.5$  and 2.0, the compacts did not disaggregate, but they did release drug more quickly than at  $\mu = 0$  and 0.1.

For the binary compacts made with the AG HPC (Fig. 4), disaggregation occurred only in the  $\mu = 1.0$  solution. At  $\mu = 1.5$ , the compacts had faster drug release than in water. In the other

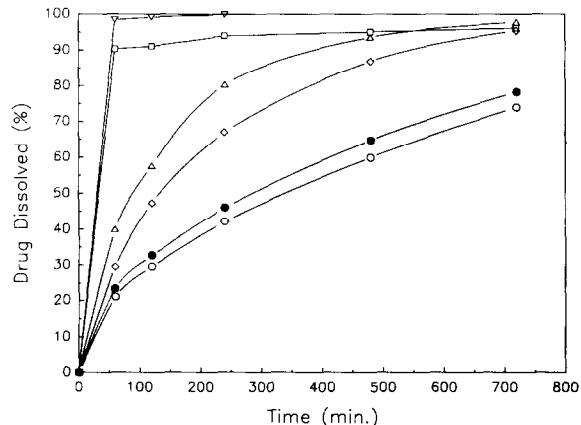


Fig. 3. Dissolution of HPC-A/PPA compacts in various ionic strength NaCl solutions ( $n = 3$ ). (●) Water; (○)  $\mu = 0.1$ ; (▽)  $\mu = 0.5$ ; (□)  $\mu = 1.0$ ; (△)  $\mu = 1.5$ ; (◇)  $\mu = 2.0$ .

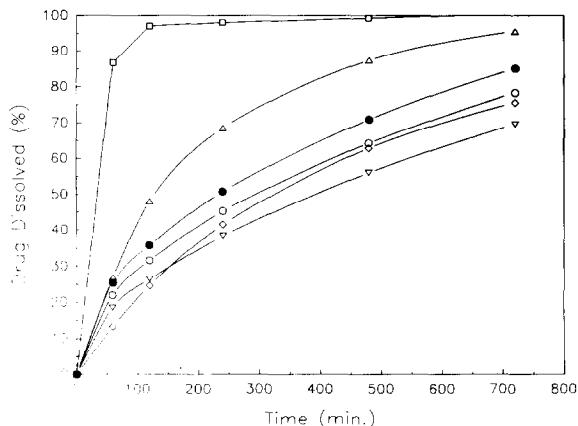


Fig. 4. Dissolution of HPC-AG/PPA compacts in various ionic strength NaCl solutions ( $n = 3$ ). (●) Water; (○)  $\mu = 0.1$ ; (▽)  $\mu = 0.5$ ; (□)  $\mu = 1.0$ ; (△)  $\mu = 1.5$ ; (◇)  $\mu = 2.0$ .

ionic strength solutions the compacts had slower release than in water.

For the binary compacts made with the AS HPC (Fig. 5), disaggregation occurred at  $\mu = 0.5$ . Although drug release was also rapid at  $\mu = 1.0$ , the compact did not disaggregate. At all the other ionic strengths, the dissolution rates were slower than in water. Therefore, for the A series of HPC, the fine particle size HPCs offer greater protection than coarse HPC against disaggregation from ionic solutions. Also, milled HPC appeared to be less susceptible to disaggregation

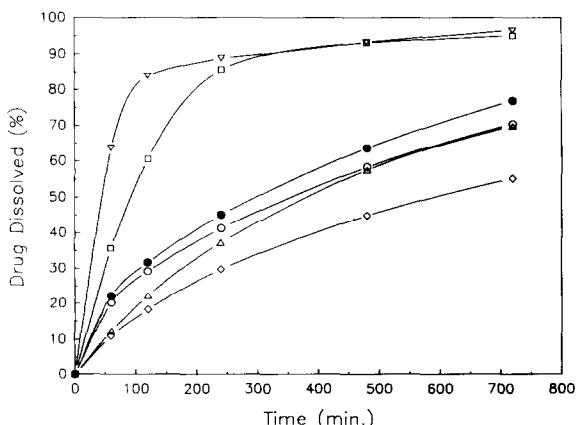


Fig. 5. Dissolution of HPC-AS/PPA compacts in various ionic strength NaCl solutions ( $n = 3$ ). (●) Water; (○)  $\mu = 0.1$ ; (▽)  $\mu = 0.5$ ; (□)  $\mu = 1.0$ ; (△)  $\mu = 1.5$ ; (◇)  $\mu = 2.0$ .

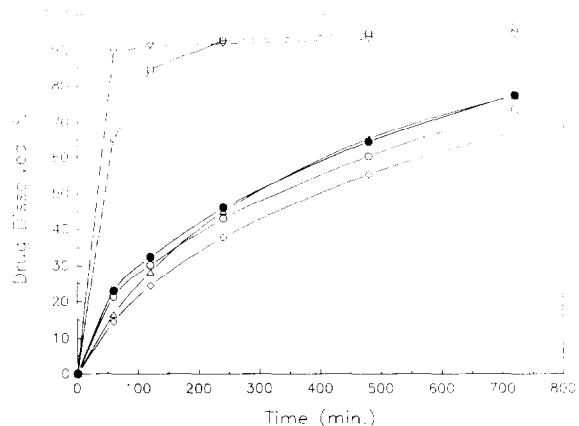


Fig. 6. Dissolution of HPC-BS/PPA compacts in various ionic strength NaCl solutions ( $n = 3$ ). (●) Water; (○)  $\mu = 0.1$ ; (▽)  $\mu = 0.5$ ; (□)  $\mu = 1.0$ ; (△)  $\mu = 1.5$ ; (◇)  $\mu = 2.0$ .

than the sieved HPC. The AS series compacts exhibited disintegration in two cases whereas the AG series exhibited disintegration in only one instance. Although this is not an overwhelming difference it does demonstrate that the AG polymer maintains its integrity at a key ionic strength level, namely,  $\mu = 0.5$ , which is closer to physiological conditions than  $\mu = 1.0$ . The dissolution results support the results from the disintegration tests.

A comparison of the different molecular weight grades of HPC which were made by sieving indicated that the BS HPC (Fig. 6) was similar to AS. However, the CS grade did not disaggregate at any of the ionic strengths. For the CS HPC (Fig. 7), as the ionic strength increased, the dissolution rate decreased.

Since the number of dissolution curves collected was large and it was difficult to compare the curves simultaneously, the AUC for each dissolution curve was calculated. This permitted quantitative characterization of an entire dissolution curve with a single number. The AUC value was directly related to the rate of drug release from the compact. The larger the AUC value, the more rapid the dissolution rate. Conversely, the smaller the AUC, the slower the release of drug. The AUC values for all the individual dissolution curves vs the ionic strength are summarized in a single graph (Fig. 8).

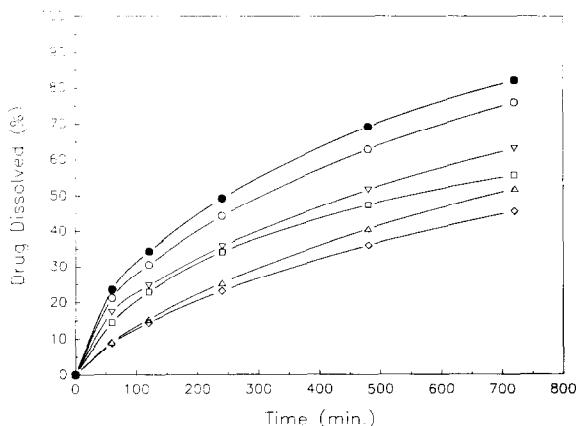


Fig. 7. Dissolution of HPC-CS/PPA compacts in various ionic strength NaCl solutions ( $n = 3$ ). (●) Water; (○)  $\mu = 0.1$ ; (▽)  $\mu = 0.5$ ; (□)  $\mu = 1.0$ ; ( $\Delta$ )  $\mu = 1.5$ ; ( $\diamond$ )  $\mu = 2.0$ .

Fig. 8 shows that the AS and BS HPCs behaved similarly, but had slower overall dissolution rates than the A HPC. By grinding the A grade to AG, the HPC is protected from disaggregation at  $\mu = 0.5$ . The AUC for CS HPC demonstrated that this grade of HPC was independent of the disaggregation effect of ionic strength changes on the binary compacts and that it had the slowest overall dissolution rate of all the polymers tested.

By adding all of the AUCs for each type of HPC over the entire range of ionic strengths studied, the following overall dissolution ranking of the HPCs was determined: A  $\gg$  BS  $\cong$  AG  $>$  AS  $\gg$  CS. Thus, the A HPC had the most rapid dissolution and CS HPC the slowest.

In contrast to the work of Fagan et al. (1989), this study showed that disaggregation did not occur at  $\mu = 0.1$  for any of the HPC types tested. In addition, by reducing the particle size by milling, the disaggregation was delayed until  $\mu = 1.0$ . Also, a decrease in the molecular weight

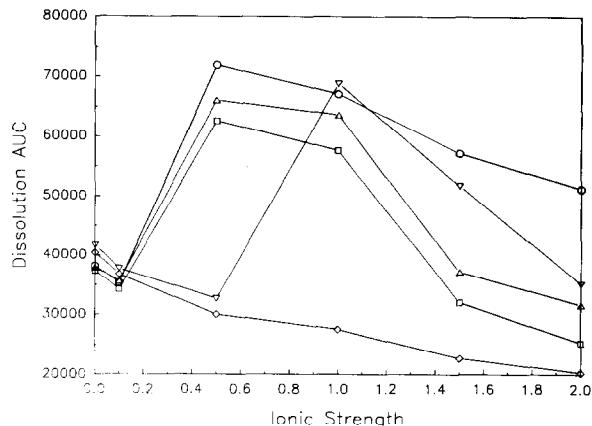


Fig. 8. Dissolution AUC of various HPC/PPA compacts at different ionic strength NaCl solutions ( $n = 3$ ). (○) A HPC; (▽) AG HPC; (□) AS HPC; ( $\Delta$ ) BS HPC; ( $\diamond$ ) CS HPC.

from the AS type to the CS prevented disaggregation from occurring at any ionic strength.

The results in this study differed from those of Fagan et al. (1989) for two reasons. Firstly, Fagan and co-workers used a formulated dosage form. In the current study, pure and binary compacts of HPC were used to minimize the effect of other excipients in the attempt to isolate and study the behavior of HPC. Fagan and co-workers may have seen premature disaggregation as a result of using a formulated tablet. Secondly, and more importantly, coarse particle size HPC is more susceptible to premature disaggregation than finer particle size HPC, as demonstrated in this investigation. Fine particle size HPC is the preferred material for hydrophilic, sustained release, matrix formulations due to its high compactibility and more rapid hydration. This is a result of the higher surface area. Fagan and co-workers used a coarse particle size HPC which resulted in premature disaggregation at  $\mu = 0.1$ .

TABLE 4

*Electrolyte composition of gastrointestinal fluids*

Fluid	Sodium (meq/l)	Potassium (meq/l)	Chloride (meq/l)	Bicarbonate (meq/l)	Total ionic strength range
Gastric	10-115	1-35	8-155	0-15	0.010-0.160
Intestinal	72-150	2-10	45-131	20-40	0.070-0.166

Mitchell et al. (1990) referred to disaggregation as the 'burst effect' and showed that this occurred for HPMC as the ionic strength was increased. However, they did not pursue higher ionic strengths than those which caused disaggregation and did not observe the subsequent decrease in the dissolution rate. Mitchell et al. described the initial decrease in dissolution rate, seen in this study from  $\mu = 0$  to 0.1 (and higher for AG and CS HPC), as being caused by thermal gelation. However, HPC does not undergo thermal gelation. Therefore, it is unlikely that this is the reason for the initial dissolution decrease observed with HPMC or HPC compacts.

Table 4 lists the ionic strengths of gastric and intestinal fluids (Collins, 1983; Gilman et al., 1985; Goldberger and Brensilver, 1986). Within the normal ranges of gastric and intestinal ionic strengths,  $\mu = 0.01$ –0.2, it is unlikely that HPC compacts would undergo premature disaggregation *in vivo*.

Although the ionic strengths of the solutions used in this study exceeded the physiological ionic strength conditions in the human gastrointestinal tract, they were used in an attempt to determine the behavior of HPC at low and moderate ionic strength solutions. The intention was to take the polymer through a complete continuum of physical changes from swelling and gelling, through swelling alone, and finally, to relative immobility. In this way, the drug release characteristics and polymer behavior could be observed under all these conditions.

## Conclusions

The ionic strength of the medium affects the disintegration and dissolution characteristics of the matrices because HPC undergoes a continuum of changes in its hydration state.

At  $\mu = 0$  and 0.1, HPC swells and gels rapidly. Thus, a strong gel layer forms on the surface of the compact which resists disaggregation and allows the drug to diffuse through.

At  $\mu = 0.5$ –1.0, the water present is less able to fully hydrate the polymer. Thus, the polymer only hydrates enough to swell. This caused the

disintegrating effect to occur which increased surface area of the compact and accelerated drug release.

When the ionic strength reached a level where even polymer swelling was restrained, the compact retained much of its original shape without gelling nor swelling, and the drug had to leach out of the compact.

Fine particle size HPC was more resistant to the influences of ionic strength changes as was lower molecular weight HPC. The results of the study indicate that at normal physiological ionic strengths, HPC compacts remain intact and release drug slowly.

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