DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(9), 1235-1248 (1988)

DISINTEGRATING AGENTS IN HARD GELATIN CAPSULES. PART II: SWELLING EFFICIENCY.

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The wicking and swelling properties of pure disintegrants were investigated from plugs prepared under conditions similar to those used in encapsulation of powder mixtures into hard gelatin capsules. Pure AcDiSol exhibited the greatest wicking and swelling action followed by Primojel, Polyplasdone-XL 10 and corn starch. The swelling properties of pure disintegrants correlated best with the swelling of formulation mixtures and the efficiency of these materials in enhancing the dissolution of hydrochlorothiazide. A change in the penetrating liquid from dilute acid to water altered the liquid uptake and swelling of AcDiSol and Primojel but not those of Polyplasdone-XL 10 and corn starch. The extent of swelling per unit volume of liquid absorbed, defined as the swelling efficiency, varied with time and type of disintegrant. The swelling efficiencies of pure AcDiSol and corn starch were unaffected by the nature of the penetrating liquid while Primojel and Polyplasdone-XL 10 exhibited greater efficiencies in water than in dilute acid. All disintegrants lost part of their efficiency when incorporated in capsule

formulations, especially in very hydrophilic matrices. The rate of wicking action could be a limiting step in the rate and extent of swelling of a disintegrant and hence hinder its efficacy in hard gelatin capsules.

INTRODUCTION

Drug dissolution from encapsulated dosage forms can be improved significantly with the addition of disintegrating agents into the formulation (1). These agents promote liquid penetration and cause swelling of the capsule plug, thus reducing disintegration and dissolution times. Previous work (2) has shown that the efficacy of disintegrants in hard gelatin capsules is dependent on the level of disintegrant employed, the nature of the matrix and the lubricant level. A significant interaction was found between these variables as well as with the degree of compaction of the encapsulated powder.

More recent studies (3) have shown that the mechanism of action of disintegrants is by rapid liquid absorption and swelling of disintegrant particles which fill the void spaces and cause the compact to disintegrate rapidly. Disintegrants, however, varied widely in their wicking and swelling properties and a minimum concentration of disintegrant was necessary to produce primary particles upon disintegration and effectively improve drug dissolution. This study was thus designed to examine the behavior of disintegrants in their pure state and in hard gelatin capsule formulations. The intrinsic ability of disintegrants to absorb water and swell was measured and related to drug dissolution from powder mixtures containing these disintegrants.

EXPERIMENTAL

Materials and Formulations

The representative disintegrants studied were croscarmellose sodium, Type A NF (AcDiSol, FMC Corp., Philadelphia, PA), sodium starch glycolate NF (Primojel, Generichem Corp., Little Falls, NJ), crospovidone NF (Polyplasdone-XL 10, GAF Corp., New York, NY) and corn starch (Anheuser-Busch Inc., St. Louis, MO). These disintegrants were tested either alone or incoporated into capsule formulations. The encapsulated systems investigated were either dicalcium phosphate dihydrate USP (Stauffer Chemical Co., Westport, CT), or anhydrous lactose USP (Sheffield Products, Memphis, TN), with 0.75% and 2.0% magnesium stearate (Amend Drug & Chemical Co., Irvington, NJ), respectively. Hydrochlorothiazide (Industria Chimica Profarmaco, Milano, Italy) was employed as a low dose drug with limited water solubility. Batches of 500 grams were blended in a 2-quart V-blender for 15 minutes and the powder mixtures were filled into size No.1 hard gelatin capsules using an automatic capsule filling machine (Zanasi LZ-64) instrumented to measure compression and ejection forces (4).

Physical Properties of Disintegrants

The true density of disintegrants was determined in a 10ml pycnometer using hexane as the non-solvent liquid while particle size was measured with an air permeability apparatus (Sub-Sieve Sizer Model 95, Fischer Scientific Co., Pittsburgh, PA). Moisture content was determined gravimetrically in a vacuum oven by drying the materials at 80^{o}C until there was no further decrease in the weight of the sample. Poured bulk densities were determined by means of a Scot Volumeter (Fischer Scientific Co., Fair Lawn, NJ), and tapped bulk densities were measured with the Univ. of Maryland rate of packing apparatus by tapping the sample 100 times. All determinations were performed in triplicate.

Disintegration and Dissolution Tests

Capsule disintegration was performed according to the USP disntegration test for hard gelatin capsules in 900 ml of 0.1 N HCl and 37°C. Drug dissolution was carried out according to USP method II, with the paddles rotating at 50 rpm. The medium was 900 ml of 0.1 N HCl maintained at 37°C and the capsules were prevented from floating with the aid of stainless steel spirals. A multiple dissolution apparatus (Hanson Research Corp., Northridge, CA) was coupled to a multiple flow cell spectrophotometer Beckman Instruments, Columbia, MD) and drug dissolution of six capsules was determined at 272 nm.

Liquid Uptake and Swelling Measurements

A liquid penetration apparatus (Fig. 1) coupled with an LVDT was employed to measure the liquid uptake and swelling of powder compacts, as previously described (3). The penetrating liquid was either 0.1N HCl or distilled water. Formulation compacts employed in these experiments were prepared in the capsule machine, using 300N of compression force. The funnel was sectioned (the two pieces held together with a bracket), and the powder compact contained in the lower end was removed before the ejection event. Compacts of pure disintegrants were prepared by placing the appropriate quantity of powder into the sectioned end of the funnel and compressed with the aid of the instrumented capsule piston and the compaction mechanism of an air permeability apparatus (Sub-Sieve Sizer® Model 95, Fisher Scientific Co., Instruments Div., Pittsburgh, PA). Compacts of 15mm height were prepared at either 200N compression force or at 40% porosity. Porosities were calculated from the dimensions of the compact and the true densities of the material. All experiments were carried out at room temperature and at least in triplicate.

RESULTS AND DISCUSSION

Disintegrants, when studied under a variety of encapsulated systems (3), demonstrated a wide range of wicking and swelling

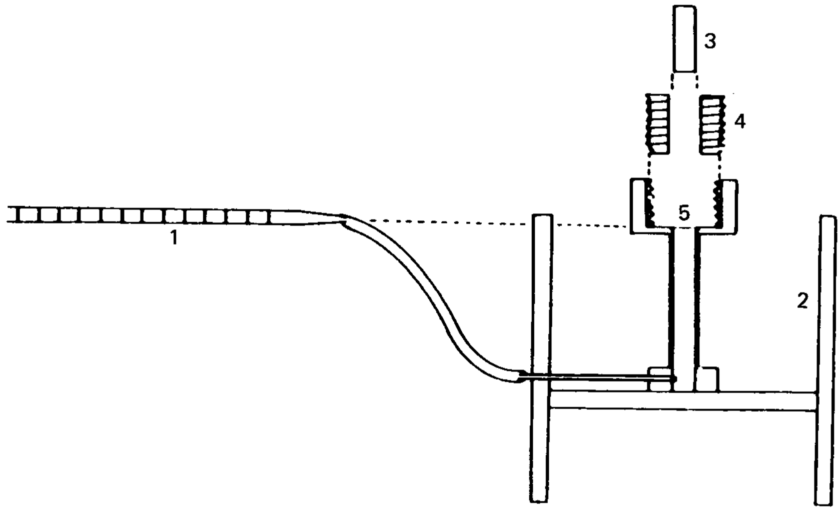

FIGURE 1

Schematic diagram of the liquid penetration apparatus.

Key: 1-graduated pipette, 2-water bath, 3-funnel section, 4-funnel holder, 5 perforated disc

properties which appeared to be concentration related. The inherent ability of these agents to sorb liquid and swell could be affected in highly porous compacts by the presence of air, very tortous pathways and possible isolation of disintegrant particles within the matrix. The properties of disintegrants, alone and in hard gelatin capsule formulations, were evaluated by liquid uptake and swelling measurements and related to drug dissolution. The disintegrants investigated in this study represent four distinct classes of disintegrants, i.e., modified celluloses, modified starches, crospovidone and corn starch. As shown in Table 1, these materials vary greatly in their physical properties. These properies as well as the method of preparation of pure disintegrant compacts could have an effect on the ability of the material to absorb water and swell. Compacts of various disintegrants were prepared either at 40% porosity (approximating the porosities of encapsulated formulations) or at 200N compression force. The volumetric uptake and swelling of

Table 1. Physical properties of pure disintegrants.

Disintegrant	Particle Size (u)	True Density (g/cc)	Poured Density (g/cc)	Tapped Density (g/cc)	Moisture Content (%)
AcDiSol	15.9	1.482	0.325	0.441	8.15
Primojel	25.2	1.503	0.662	0.788	8.32
Polypl. XL-10	8.1	1.179	0.265	0.350	4.78
Corn Starch	11.4	1.459	0.432	0.630	10.80

these compacts were measured using 0.1 N HCl as the penetrating liquid. As shown in Figure 2A, the differences in the rate of liquid penetration, under the two methods of compact preparation, are negligible for disintegrants other than AcDiSol which demonstrated slightly faster liquid uptake in compacts of 40% porosity than in compacts compressed at 200N. It should be noted that AcDiSol has a very low tapped density and it exhibits a high degree of elastic recovery after compaction. Particles that exist under great stress and have deformed may, upon contact with the penetrating liquid, relieve the stress by disrupting the bonds and returning to their original shape, thereby causing the compact structure to open up. The differences observed in liquid penetration were also present in the swelling of the compacts, greater penetration corresponding to greater swelling (Fig. 2B).

Comparison of Pure Disintegrants

AcDisol exhibited the greatest wicking action and swelling of the materials tested, followed by Primojel. Corn starch compacts were completely wetted within three minutes, showing only minimal

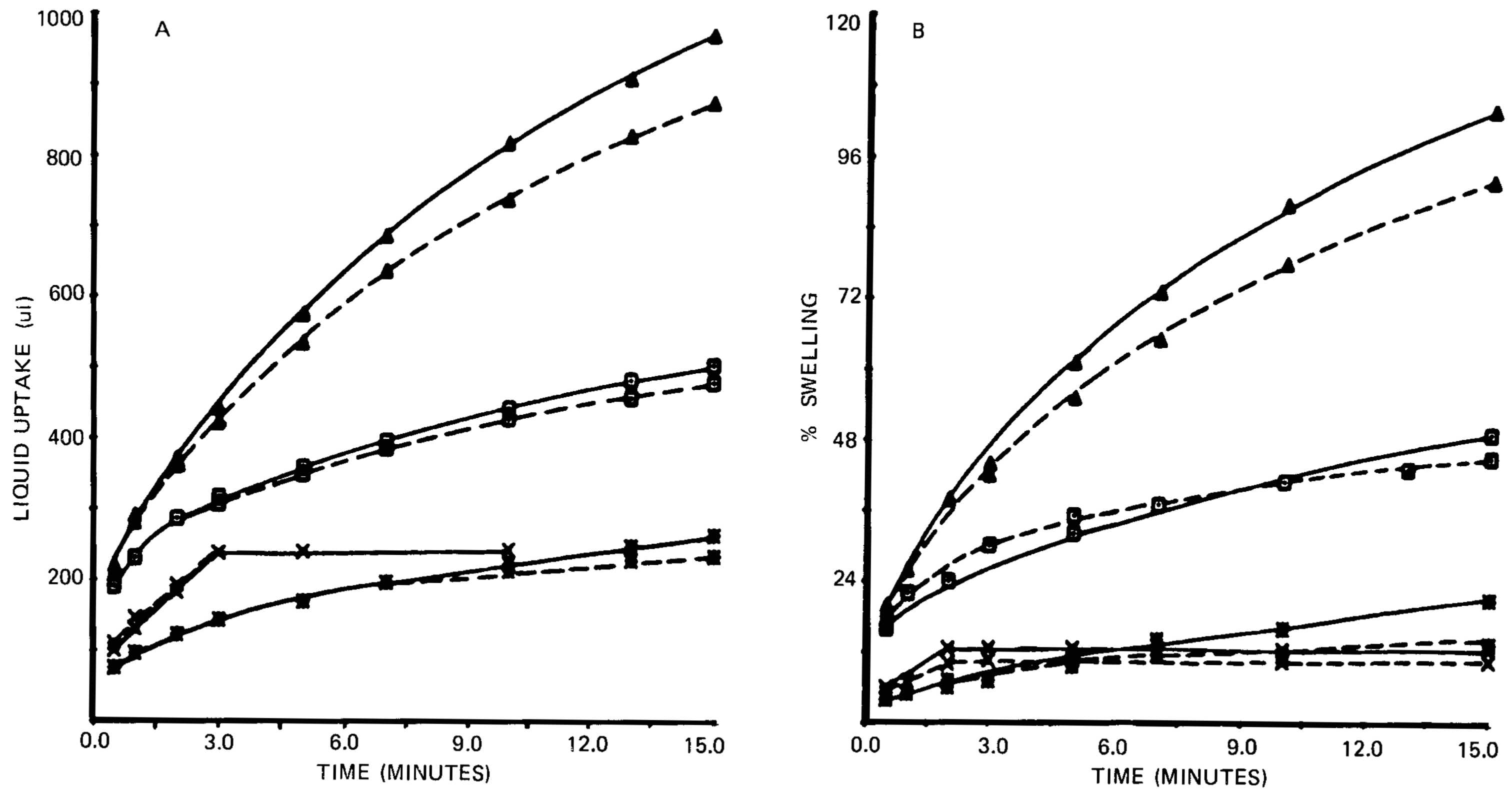

FIGURE 2

Liquid uptake of 0.1N HCl and swelling of pure disintegrant compacts prepared at 200N compression force (---) or at 40% porosity (——). Key: (▲) AcDiSol, (⊡) Primojel, (✱) Polyplasdone-XL10, (X) corn starch

Table 2. Effect of 7% disintegrants (10% corn starch) on various physical properties and hydrochlorothiazide dissolution from dicalcium phosphate based capsules.

Disintegrant	Disint. (min.)	Drug Released (40 Min.)	Liquid Uptake (5 Min.)	% Swelling (5 Min.)
AcDiSol	3.09 (0.19)	90.2 (0.64)	159 (1.28)	11.9 (0.29)
Primojel	4.28 (0.15)	73.1 (0.89)	77.4 (2.24)	7.06 (0.24)
Polyplasdone	6.57 (0.37)	54.9 (1.57)	81.0 (2.15)	2.34 (0.08)
Corn Starh	9.43 (0.35)	40.4 (1.48)	34.0 (0.53)	0.48 (0.03)

( )=SEM

swelling. Polyplasdone-XL 10, on ther hand, absorbed liquid slower than corn starch initially, but its liquid uptake continued to increase and appeared to exceed that of corn starch. Similar observations can be made about the swelling of these two disintegrants. The liquid uptake and swelling results of pure disintegrants correlated only partially with the results obtained when disintegrants were incorporated in a formulation (Table 2). For instance, pure Primojel absorbed significantly higher amounts of liquid than pure Polyplasdone-XL 10 while their effect on liquid penetration into the formulations was similar. Furthermore, while pure Polyplasdone-XL 10 sorbed liquid at a slower rate than corn starch, the opposite was true when the disintegrants were incorporated in encapsulated systems. It is evident that Primojel and corn starch lose part of their wicking efficacy when included in an insoluble and hydrophobic matrix. The swelling properties of pure disintegrants, however, correlated well with the swelling of formulation compacts containing these disintegrants and their ability to enhance drug dissolution.

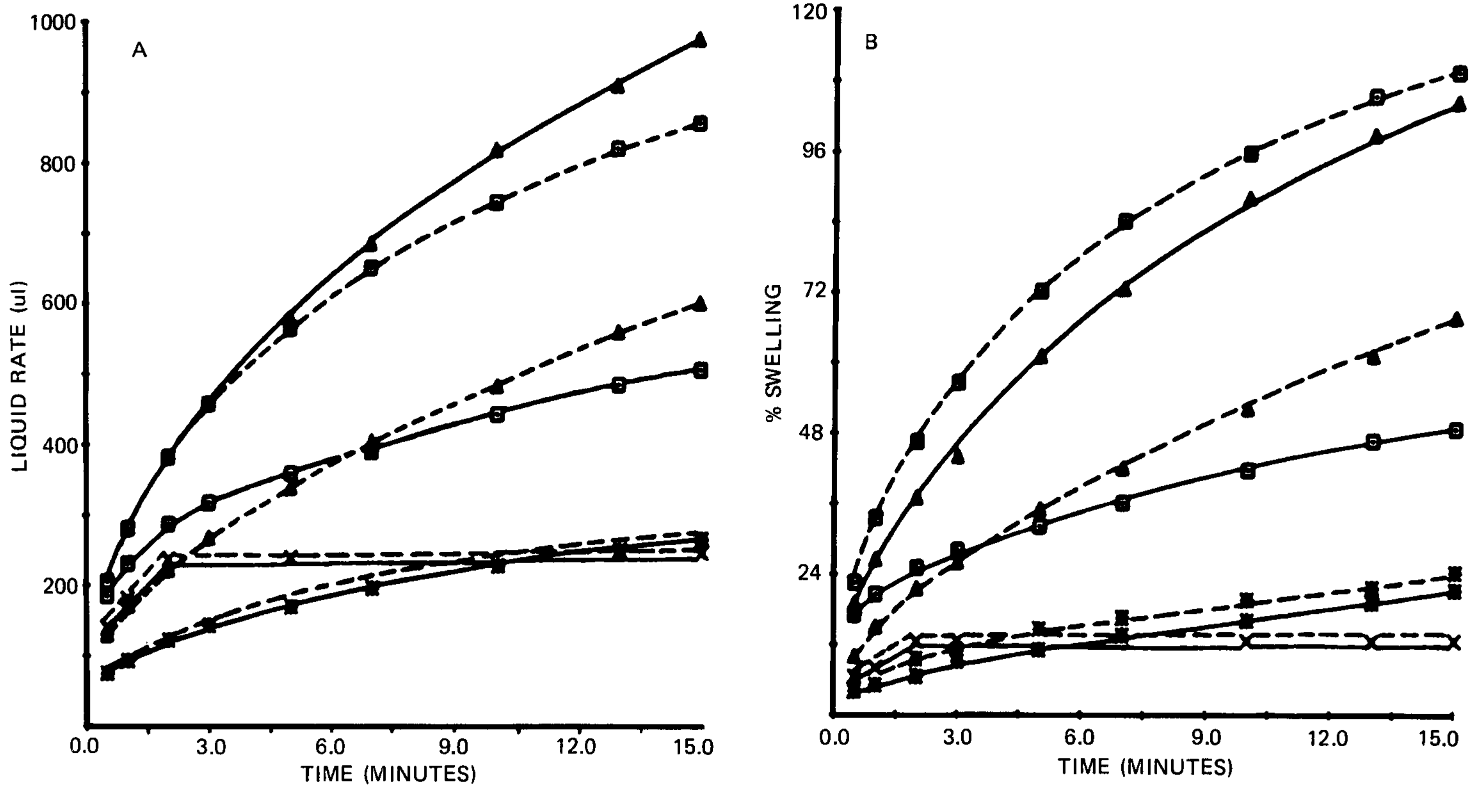

FIGURE 3

Liquid uptake and swelling of pure disintegrants, using 0.1N HCl (——) or water (---) as the penetrating liquid (40% porosity).

Key: (▲) AcDiSol, (⊡) Primojel, (✱) Polyplasdone-XL 10, (X) corn starch

Effect of Penetrating Liquid

The medium employed for drug dissolution or liquid penetration into powder compacts has been reported (5) to influence the performance of disintegrants. These investigators, however, studied only the extent of swelling of disintegrant dispersions. To date no study has been made of the effect of pH on the rate of liquid uptake of disintegrants which, in turn, affects the rate of swelling. Compacts of pure disintegrants of approximately 40% porosity were used for this study, employing either water or dilute hydrochloric acid as the penetrating liquid. The results of liquid uptake (Fig. 3A) indicate that the rate of liquid penetration into AcDiSol compacts is significantly faster with dilute HCl than with water. Furthermore, the opposite is observed with Primojel; that is, an increase in the environmental pH enhances the rate of liquid uptake into the compact. The pH does not appear to affect the liquid uptake of either Polyplasdone-XL 10 or corn starch. The swelling of disintegrants is affected in a similar fashion (Fig. 3B). This implies that a change in dissolution medium could cause significant changes on drug dissolution by enhancing or decreasing the liquid uptake into the dosage form which in turn, along with changes in the swelling of the disintegrant, will affect disintegration of the powder mass. The effect of pH on the properties of a disintegrant like Primojel could have even more serious implications on the in-vivo availability of the active entity, since the dosage form is first exposed to the stomach fluids with a very low pH. The efficiency of Primojel could be drastically reduced under such conditions and result in slow drug release from a formulation which exhibited excellent in-vitro drug dissolution when tested in water.

Swelling Efficiency of Disintegrants

For any one disintegrant, swelling of the compact appeared to be proportional to the amount of liquid taken up into the powder bed. Lack of correlation with the dissolution results, however, suggests that the intrinsic properties of the disintegrants could be seriously altered in an encapsulated powder mixture. An indicator of a disintegrant's ability to absorb liquid and thus swell could be obtained by normalizing compact swelling, at a particular time, for the volume of liquid taken up into the compact. This is defined as the swelling efficiency of disintegrants. The data are plotted as the percent swelling per unit volume of liquid sorbed versus time. The swelling efficiency of disintegrants, either alone or in formulations, is shown in Figure 4. Ideally, the swelling efficiency of disintegrants should be constant with time; any changes indicate that the rate of swelling is not always proportional to the rate of liquid uptake as penetration proceeds. An increase in the swelling efficiency means that swelling occurs faster than liquid is drawn into the compact. In such cases, expansion of the powder bed is caused partly by breaking the bonds and/or elastic recovery of the compact and partly by swelling of the disintegrant particles. A decrease in the swelling efficiency results from changes in the structure of the compact which make the disintegrant particles inaccessible to the penetrating liquid, changes in the viscosity of the liquid due to dissolution of some components of the powder mixture, and gellation of disintegrant particles.

The plots shown in Figure 4 reveal some interesting phenomena about the behavior of disintegrants. Looking at the swelling efficiency of pure disintegrants, it is observed that AcDiSol and corn starch are unaffected by the type of penetrating liquid while Primojel and Polyplasdone-XL 10 exhibited greater efficiencies in water. Considering these findings together with the the results shown in Figure 3, it is obvious that both the rate and extent of swelling of a disintegrant could be affected by the pH of the penetrating liquid. For instance, with AcDiSol more liquid is drawn into the compact at low pH and there is proportionately greater swelling. With Primojel, water is drawn into the compact faster than dilute acid, but Primojel particles also swell to a greater extent in the presence of water. Similar observations can be made about the other two disintegrants. The swelling efficiencies of of AcDiSol and Primojel in dilute acid are approximately equivalent and

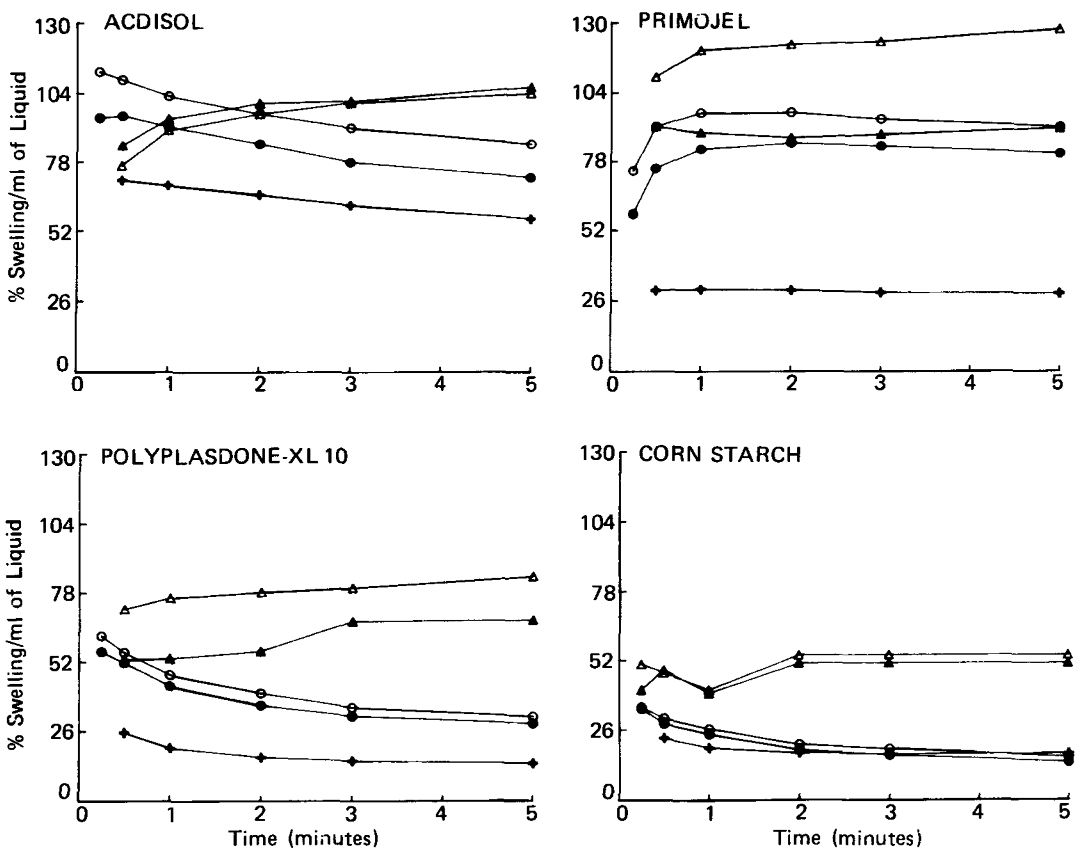

FIGURE 4

Swelling efficiency of disintegrants under various conditions, either alone or incorporated in capsule formulations.

Key: ▲: Pure disintegrant, 40% porosity, 0.1N HCl

△: Pure disintegrant, 40% porosity, water

●: Dical.phosph., 7% disint.(10% starch), 0.1N HCl, 100N force

○: Dical.phosph., 7% disint.(10% starch), 0.1N HCl, 300N force

+: Lactose, 3% disintegrant (10% starch), 0.1N HCl, 300N force

significantly greater than those of Polyplasdone-XL 10 and corn starch. AcDiSol nonetheless sorbs liquid and swells at a faster rate than pure Primojel (Fig. 3). Primojel, however, exhibits the greatest swelling efficiency of all disintegrants in water.

When incorporated in encapsulated systems, with dilute acid as the liquid, all disintegrants lost part of their swelling efficiency. This is mainly due to isolation of disintegrant particles within the matrix and increased viscosities that occur upon dissolution of some particles. The most dramatic decrease in the swelling efficiency of disintegrants (especially Primojel) occured in anhydrous lactose formulations; these systems are hydrophilic and very water soluble. When incorporated in dicalcium phosphate formulations, less dramatic losses in efficiency were observed with all disintegrants. AcDiSol and Primojel clearly appeared to be superior to the other disintegrants. These disintegrants also showed higher efficiency at the higher levels of compaction; these results support previous findings (3) which showed that at lower porosities there is more structure for disintegrants to swell against, thus resulting in faster disintegration and dissolution times.

The performance and properties of disintegrants in a dosage form rather than in their pure state are of more importance in optimizing drug dissolution, especially with drugs of low water solubility. Swelling efficiencies indicate the ability of the disintegrant to swell in the presence of liquid, provided the liquid is available. These measurements when contrasted with liquid uptake and swelling of the compacts (Table 2) clearly demonstrate that the rate of wicking could become the limiting step in the swelling efficiency and hence the efficacy of the disintegrant. Primojel certainly is a case in point; its swelling efficiency in acid is as good as that of AcDiSol, yet its rate of liquid uptake and swelling as well as its effect on drug release are markedly lower than that of AcDiSol.

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