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DISINTEGRATING AGENTS IN HARD GELATIN CAPSULES. PART I: MECHANISM OF ACTION.

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The mechanism of disintegrants in encapsulated mixtures was investigated by measurements of liquid uptake and swelling. An apparatus was designed to accomodate the capsule plugs and an LVDT was used to measure expansion of the compacts upon liquid uptake. AcDiSol, Primojel, Polyplasdone-XL 10 and corn starch, representing four distinct classes of disintegrants, were tested in anhydrous lactose and dicalcium phosphate based capsules. AcDiSol was found the most effective in improving the release of hydrochlorothiazide from dicalcium phosphate capsules, followed by Primojel, Polyplasdone-XL and corn starch. A minimum concentration was necessary to produce primary particles upon disintegration and significantly affect dissolution. Increased compaction resulted in faster disintegration and dissolution times due to higher degree of swelling of the powder compact at lower porosities. Disintegrants were less effective in the already fast dissolving lactose system. In both systems, disintegration times and compact swelling correlated best with dissolution. Extensive swelling of disintegrant particles is of primary importance for a disintegrant to be most effective.

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INTRODUCTION

Disintegrants are employed in tablets to aid dispersal of the powder mass and to maximize drug-particle exposure to the dissolution medium (1). Even though many investigators have emphasized the importance of deaggregation of encapsulated mixtures (2), only recent reports (3, 4) have advocated the use of disintegrants in hard gelatin capsules. It was reported that relatively higher levels than those normally used in tableting are needed for disintegrants to exert their effect. These studies investigated the interplay of formulation and machine variables on the efficacy of disintegrants from encapsulated systems, but only speculations were made about the mode of action of disintegrants in these highly porous compacts.

This study was thus designed to investigate the mechanism of action of disintegrants in hard gelatin capsules filled on an automatic capsule filling machine under standardized and controlled conditions. To elucidate the mechanism of disintegrant action, a liquid uptake apparatus was designed and liquid penetration and swelling measurements were performed on the capsule plugs.

EXPERIMENTAL

Materials

Dicalcium phosphate dihydrate USP, (Stauffer Chemical Co., Westport, CT), anhydrous lactose USP, (Sheffield Products, Memphis, TN), magnesium stearate (Amend Drug & Chemical Co., Irvington, NJ), hydrochlorothiazide USP (Industria Chimica Profarmaco, Milano, Italy), croscarmellose 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 NF (Anheuser-Busch Inc., St. Louis, MO) were used as received from the supplier.

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Formulations

The filler systems employed were dicalcium phosphate dihydrate and anhydrous lactose, with 0.75% and 2% magnesium stearate respectively. Disintegrants levels ranged from 0-10%, and 4% hydrochlorothiazide represented a drug with low water solubility. Batches of 500-800 grams were blended in a 2-quart V-blender for 15 minutes and the powder mixtures were filled into No.1 hard gelatin capsules using an instrumented Zanasi LZ-64 capsule filling machine (5). Capsules were prepared at various compaction forces and evaluated for disintegration and dissolution times.

Disintegration and Dissolution Tests

Both tests were performed according to USP methods for hard gelatin capsules, using 900ml of 0.1N HCl at 37°C as the medium. A dissolution apparatus (Hanson Research Corp., Northridge, CA) was coupled to a multiple flow cell spectrophotometer (Beckman Instruments, Columbia, MD) and drug dissolution from six capsules was determined at 272 nm continously. The paddles rotated at 50 rpm and the capsules were held in spirals to prevent them from floating.

Liquid Uptake and Swelling Measurements

Compacts employed in these experiments were prepared in the capsule machine. The dosator funnel was sectioned at a length of 25.55 mm from its lower end and the two parts of the funnel were connected with a bracket. After compaction of the powder plug, and before the ejection event, the machine was stopped and the funnel containing the plug was removed. A liquid penetration apparatus (Fig. 1), was designed to accommodate the funnel containing the powder compact, which stood on a perforated disc/base. Under no hydrostatic pressure, liquid was brought into cell unit through the reservoir until it just wetted the perforated disc. The volumetric uptake of 0.1N HCl into the plug was noted on the graduated pipette at various times. An LVDT (Linear Variable Differential Transducer) was employed to measure compact expansion upon liquid uptake. The LVDT was supported on a stand and its core was placed on top of the

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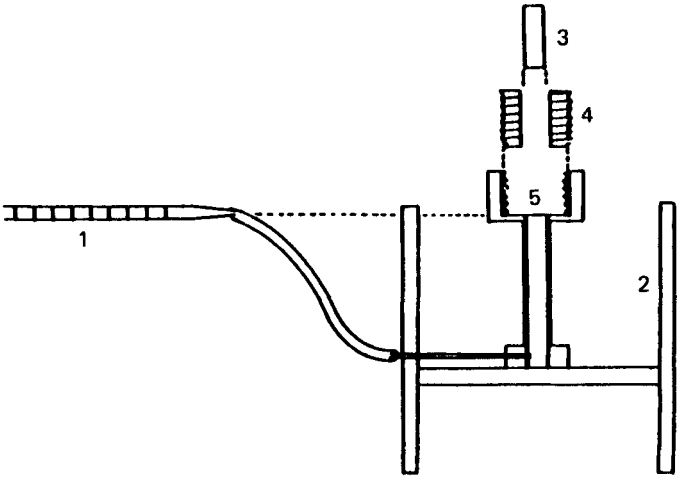

FIGURE 1

Schematic diagram of the liquid penetration apparatus.
Key: 1-graduated pipette, 2-water bath, 3-funnel section, 4-funnel holder, 5-perforated disc

compact just before starting the liquid uptake experiment. Knowing the change in height at any time and the original height, the percent of compact swelling was calculated. All liquid uptake and swelling measurements were carried at 24°C, at least in triplicate.

RESULTS AND DISCUSSION

AcDiSol was initially tested in dicalcium phosphate capsules to define an effective range of disintegrant concentrations and validate the liquid uptake apparatus. As shown in Figure 2A, all levels of AcDiSol enhance drug dissolution; however, this effect does not appear to be directly proportional to concentration. 3% AcDiSol exhibited a minimal effect on drug dissolution, and disintegration of these capsules was still prolonged (12.5 min.). It is evident that a minimum concentration of AcDiSol is required to produce rapid disintegration and drug release from these systems.

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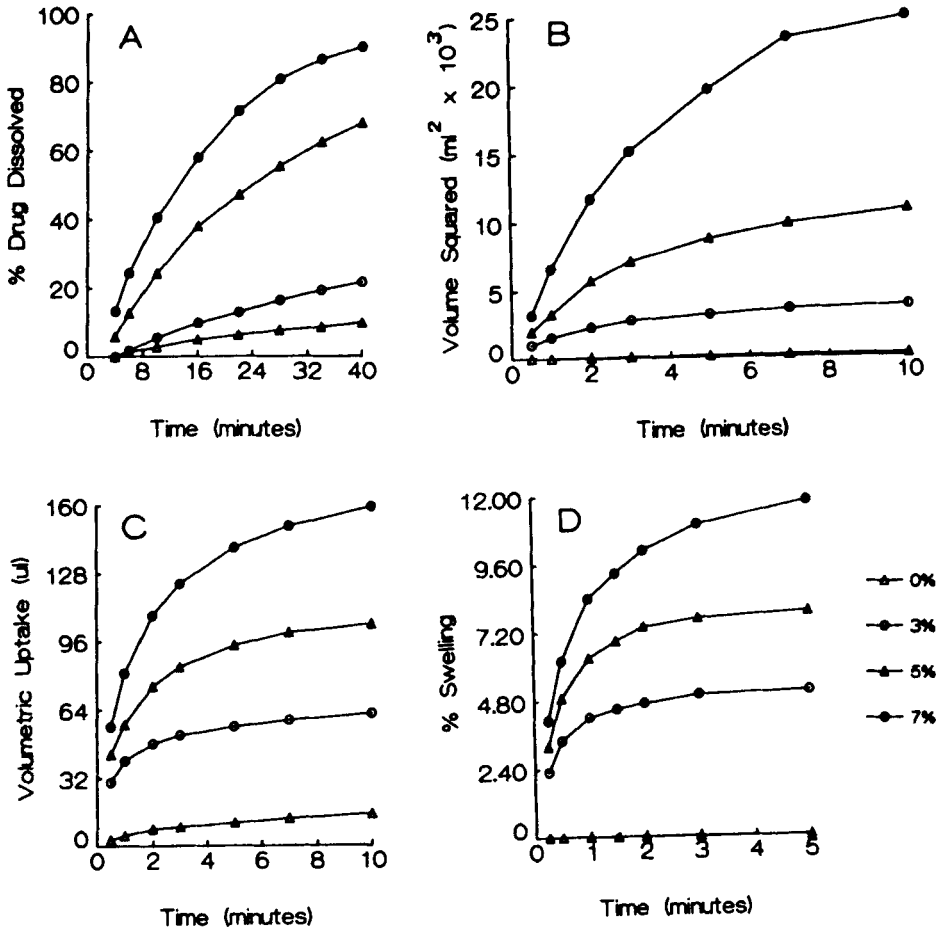

FIGURE 2

Effect of AcDiSol concentration on hydrochlorothiazide dissolution (A), liquid uptake (B & C) and swelling (D) of dicalcium phosphate dihydrate based capsules (300N force).

Liquid penetration data are generally presented according to the Washburn equation:

$$L^2 = \frac{r \cdot Y \cdot \cos\theta}{2n} \cdot t$$

where L is the length of liquid penetration, r is pore radius, Y is the surface tension of the liquid, cosθ is the contact angle of the

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liquid with the solid, n is the viscosity of the liquid and t is time. A linear relationship is expected between L^2 and t. Since the volume of the liquid is proportional to penetration length, the relation between V^2 and t is also linear. Treated in this fashion, the rates of liquid uptake into dicalcium phosphate compacts containing various levels of AcDiSol, as shown in Figure 2B, do not appear to adhere to theory. Many investigators have pointed out that this equation does not hold true if changes occur in the structure of the compact upon liquid penetration (6, 7). The systems investigated in this study consist of a long, confined plug, containing a highly swellable component. These factors, along with dissolution of some excipients will retard the rate of liquid uptake with time. When the data are plotted as volume of liquid uptake versus time (Fig. 2C), a non-linear relationship is also obtained, despite the claim of some investigators (8) that such a linear relationship exists if liquid penetration into a powder bed proceeds by laminar non-stationary flow. Regardless of how the data are treated, it is apparent that an increase in AcDiSol concentration enhances the liquid uptake into dicalcium phosphate compacts. Simple volumetric plots (Fig. 2C) indicate, however, an approximately linear relationship between AcDiSol concentration and liquid uptake. The Washburn plots (Fig. 2B), on the other hand, tend to exaggerate the differrences between curves, because of squaring of the volumetric uptake and complicate interpretation of the results. Thus, it was decided to treat the data as a simple volume versus time relationship.

Swelling of the disintegrant particles causes expansion of the compact (Fig. 2D) and this effect is proportional to the disintegrant concentration in the powder mixture. The rate of swelling is very fast initially, leveling off after a few minutes, probably due to confinement of the plug and changes in the viscosity of the penetrating liquid. An excellent correlation exists between the concentration of AcDiSol and the swelling and liquid uptake data (Fig. 2C). However, as previously noted, the effect of AcDiSol on disintegration and dissolution times is not directly proportional to

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its concentration in the formulation. This observation may be explained by the fact that although AcDiSol may sorb liquid and cause swelling of the compact in proportion to the amount added, sufficient disintegrant must be present to expose primary particles upon disintegration. Too few disintegrant particles per unit volume of compact may only lead to the production of larger aggregates which will have difficulty in further deaggregation.

Disintegrants in Dicalcium Phosphate Based Capsules

Based on the preliminary findings, AcDiSol, Primojel and Polyplasdone-XL were compared at 5% and 7% levels against 10% corn starch. The dissolution results from capsules containing 5% disintegrant, shown in Figure 3A, indicate that drug release was improved in all cases over the control. AcDiSol was found the most effective in enhancing drug release from these systems, producing capsules that disintegarted in approximately 5 minutes. Primojel, Polyplasdone-XL 10 and corn starch all generated similar dissolution profiles; drug release from these formulations was still quite prolonged and correlated well with lengthy disintegration times of about 10 minutes. The effect of 5% disintegrants on liquid penetration and swelling of these compacts is depicted in Figures 3B and 3C. These results indicate that compacts containing 5% AcDiSol sorbed much higher amounts of liquid into the powder mixture and swelled to a greater extent than compacts containing any of the other disintegrants. The differences in these parameters between the Primojel, Polyplasdone-Xl 10 and corn starch systems did not manifest themselves in drug dissolution; evidently the long disintegration times masked these differences.

The effect of 7% disintegrant on drug dissolution is shown in Figure 4A. AcDiSol appeared, again, to be the most efficient disintegrant in enhancing drug release, followed by Primojel, Polyplasdone-XL 10 and corn starch. Disintegration times for these capsules were 3.09, 4.28, 6.57 and 9.43 minutes, respectively, which correlated well with the dissolution results. An increase in

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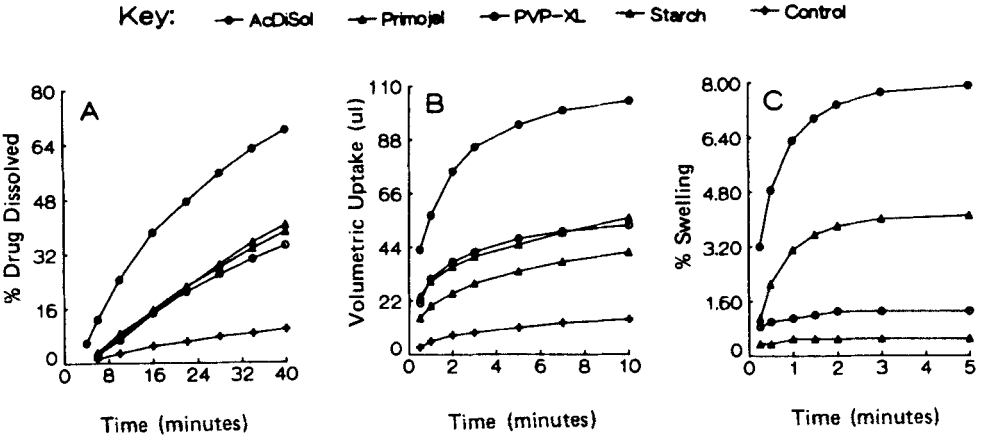

FIGURE 3

Effect of 5% disintegrant (10% corn starch) on hydrochlorothiazide dissolution (A), liquid uptake (B) and swelling (C) of dicalcium phosphate dihydrate based capsules (300N force).

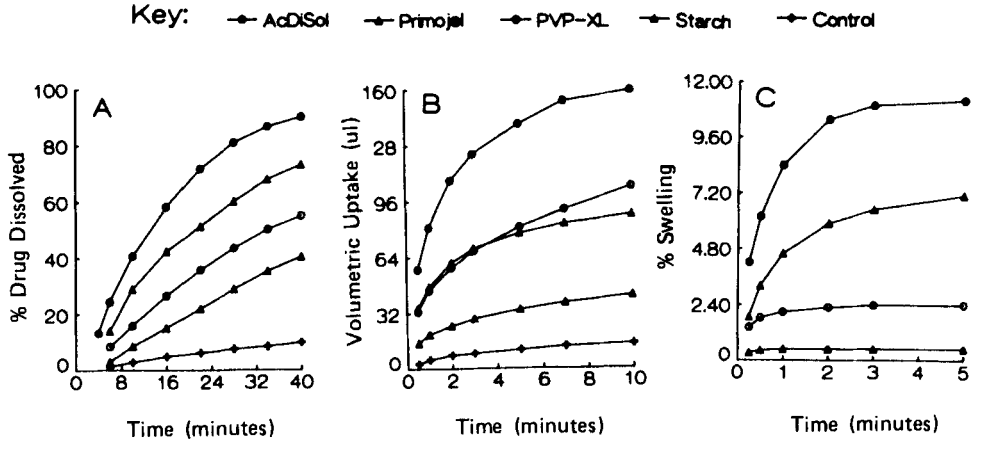

FIGURE 4

Effect of 7% disintegrant (10% corn starch) on hydrochlorothiazide dissolution (A), liquid uptake (B) and swelling (C) of dicalcium phosphate dihydrate based capsules (300N force).

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disintegrant concentration from 5% to 7% resulted in all cases in faster disintegration and dissolution rates. Furthermore, it became evident that 7% disintegrant concentration (10% corn starch) was sufficiently high to expose any differences in the efficacy of Primojel, Polyplasdone-XL 10 and corn starch as disintegrating agents. The effect of this level of disintegrants on liquid penetration and swelling of dicalcium phosphate based capsules is depicted in Figures 4B and 4C. AcDiSol was the most effective, and corn starch the least, in drawing liquid into the compact and causing swelling of the powder bed. Primojel formulations, on the other hand, swelled much more extensively than those containing Polyplasdone-XL 10, despite the fact that the liquid uptake into the Primojel compact was either similar or lower than that of Polyplasdone-XL 10. Considering the disintegration and dissolution results, wherein Primojel was more effective than Polyplasdone-XL 10, it appears that the swelling action, rather than the wicking action, of the disintegrant would be the parameter most important in affecting disintegration times and drug dissolution.

An increase in the degree of compaction of the capsule contents resulted in most instances in more rapid drug dissolution. It was theorized that at low degrees of compaction some of the swelling of disintegrants is accomodated within the voids of the structure, whereas at reduced porosities there is more structure for disintegrants to swell against, thus resulting in more rapid disintegration (4). The differences in disintegration and dissolution results due to compression force were compared by means of a simple t-test ($p < 0.05$). The disintegration results (Fig. 5A) show that increasing the compression force from 100N to 300N resulted in faster deaggregation of the capsule contents for all systems tested except the formulation containing 3% AcDiSol. Faster disintegration, in turn, promotes faster drug dissolution (Fig. 5B). The compression force effect on drug release was found to be statistically significant only with systems containing disintegrants that swell extensively, AcDiSol and Primojel in this instance; the trend, nonetheless,

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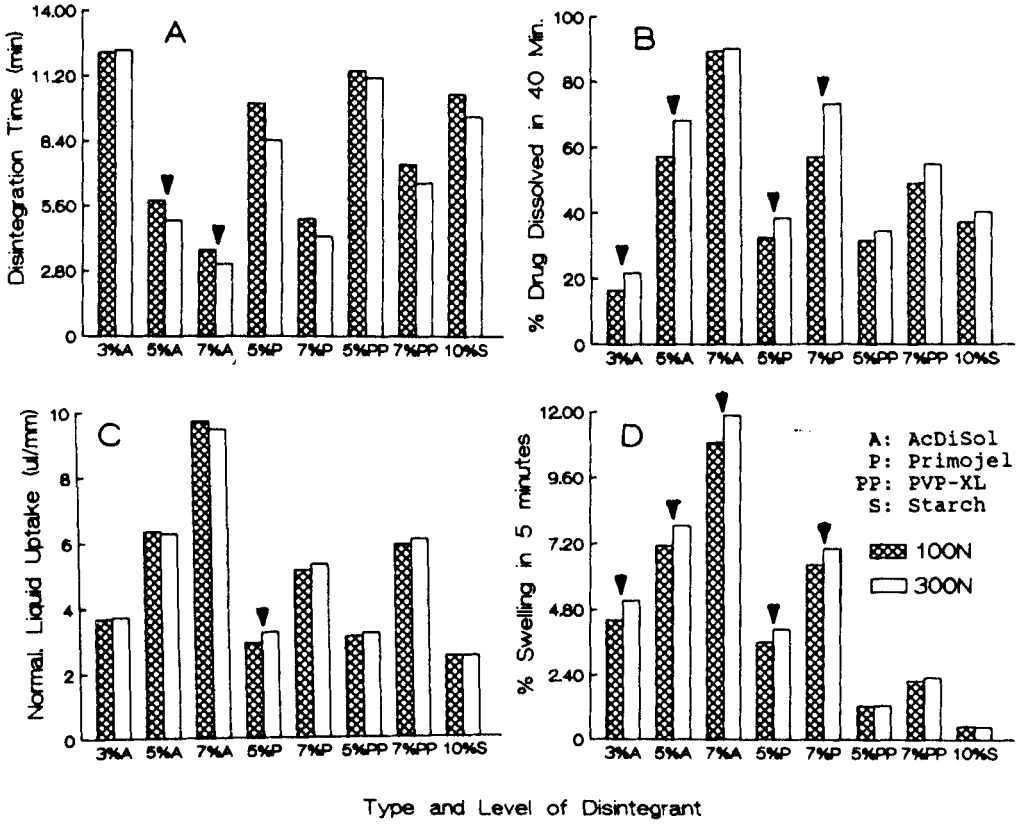

FIGURE 5

Effect of compression force on disintegration (A), hydrochlorothiazide dissolution (B), liquid uptake (C) and swelling (D) of dicalcium phosphate dihydrate based capsules containing various types and levels of disintegrants. (▼ Results between compression forces were significant at $p<0.05$).

is quite evident with all the disintegrating agents tested. This effect, however, could be overshadowed in a very fast dissolving system, as is the case with 7% AcDiSol.

The liquid uptake and swelling data for the various powder mixtures compressed at 100N and 300N, are shown in Figures 5C and 5D. The liquid drawn into the compacts at the end of ten minutes was

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normalized for plug length. Normalization of the liquid uptake data was performed to account for differences in the height of the compacts at the two compression forces. Low levels of compaction normally result in slightly higher liquid penetration into the powder bed compared to high levels, but the liquid taken up is accomodated within the more porous structure. As seen in Figure 5C a change in the degree of compaction does not produce significant changes in the liquid taken up into the compact. The results of compact swelling (Fig. 5D), on the other hand, clearly demonstrate that compacts containing disintegrants capable of extensive swelling, as is the case with AcDiSol and Primojel, exhibit higher degrees of swelling ($p<0.05$) at lower porosities of the powder bed. These findings support, at least in part, the proposed theory. The disintegration and dissolution results in Figure 5 show that drug release is also enhanced with increased compression force even in those systems containing Polyplasdone-XL and corn starch, despite the fact that liquid uptake or swelling of the compacts was relatively less sensitive to compressional changes. Additional contributing factors to the compression effect could be a higher degree of bonding between filler and disintegrant particles as well as deformation of disintegrant particles which, at higher compression forces display a greater disruptive force upon contact with the penetrating liquid. It has been demonstrated in tableting that deformation of starch grains is one mode by which starch effects tablet disintegration (9).

Disintegrants in Anhydrous Lactose Based Capsules

The effect of disintegrants in soluble matrices is lower than that in insoluble matrices, however, lesser amounts of disintegrant are needed to effect similar dissolution rates. AcDiSol, Primojel and Polyplasdone-XL 10 were therefore compared, in anhydrous lactose based capsules at the 3% level against 10% corn starch. The dissolution of hydrochlorotiazide from these encapsulated systems (Fig. 6A) indicate that there exist differences in the efficacy of these disintegrants, especially at the initial stages of the dissolution,

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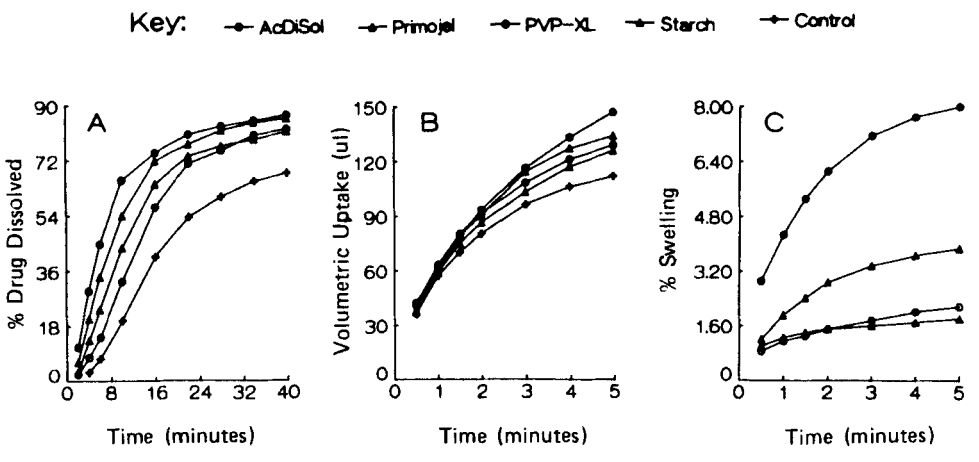

FIGURE 6

Effect of 3% disintegrant (10% corn starch) on hydrochlorothiazide dissolution (A), liquid uptake (B) and swelling of anhydrous lactose based capsules (300N force).

but these differences tend to be minimized as drug dissolution proceeds. AcDiSol and Primojel appear to be more efficient disintegrants than Polyplasdone-XL 10 or corn starch in this soluble base.

Liquid penetration into compacts of anhydrous lactose even in the absence of disintegrant, is quite rapid, indicating a very hydrophilic system (Fig. 6B). Disintegrants will nevertheless enhance liquid uptake because of their wicking action. The rate of liquid uptake into these compacts is very similar initially, but as the liquid penetration proceeds, some differences between the disintegrants are observed. Even though anhydrous lactose dissolves partially upon liquid penetration, thus increasing the viscosity of the penetrating liquid, disintegrants will counteract this effect by promoting wicking and opening up of the structure. The desintegrants demonstrate greater differences in their abilities to effect swelling (Fig. 6C) than to enhance liquid uptake. AcDiSol containing compacts swell the most, and at a faster rate, followed by Primojel, Polyplasdone-XL 10 and corn starch. The dissolution results appear to correlate best with the ability of disintegrants to cause swelling and expansion of the powder bed.

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