DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 8(3), 397-410 (1982)

An Evaluation of Croscarmellose as a Tablet Disintegrant in Direct Compression Systems

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Abstract

The disintegrant actions of croscarmellose type A (Ac-Di-Sol, FMC Corp.) and croscarmellose type B (CLD-2, Buckeye Cellulose Corp.) have been compared to that of corn starch in direct compression tablets in which microcrystalline cellulose (Avicel PH101, FMC Corp.) was the matrix. Two types of formulations were examined using either pyridoxine or hydrochlorothiazide as drug. The data clearly shows that both forms of croscarmellose are markedly superior to corn starch and are active at quite low concentrations. The CLD-2 may promote more rapid dissolution in some systems than Ac-Di-Sol.

Introduction

The increasing attention being given to biological availability and generic equivalence has further emphasized the importance of disintegrant selection and dissolution testing. Thus, it now seems probable that USP XXI will mandate dissolution tests on the majority of conventional oral tablets and capsules.

Fortunately, the pharmaceutical formulator now has available a number of disintegrants of considerable efficacy (1-5). The present paper reports studies of the disintegrant efficiency of croscarmellose types A and B (Ac-Di-Sol and CLD-2) in comparison with corn starch, which can, perhaps, be regarded as the traditional standard

tablet disintegrant. Two drugs, pyridoxine and hydrochlorothiazide, were selected for this study and microcrystalline cellulose (Avicel PH 101) was used as tablet matrix. The disintegrants were examined in formulations containing 0.25, 0.5, 1.0 and 2.0% of the three products. It has previously been suggested (2) that some formulators unaware of the full potential of modern disintegrants use excessive quantities of these substances.

The tablets prepared in this investigation were evaluated by weight, hardness, friability, disintegration and dissolution. Both the Ac-Di-Sol and CLD-2 are clearly markedly superior to corn starch. In some formulations the CLD-2 may be significantly more effective than the Ac-Di-Sol.

Experimental

The three tablet disintegrants chosen for this study were: croscarmellose type A[1], croscarmellose type B[2], and corn starch, U.S.P.[3].

The disintegrants were incorporated into formulations containing microcrystalline cellulose[4] as matrix, colloidal silicon dioxide[5] as a flow aid, stearic acid[6] as a lubricant and either pyridoxine hydrochloride or hydrochlorothiazide.[8] The two formulations used were as follows:

Pyridoxine hydrochloride	10%
Stearic acid	2%
Disintegrant	0, ¼, ½, 1 or 2%

1. Ac-Di-Sol, FMC Corporation, Phila., PA (Lot #6379)
2. CLD-2, Buckeye Cellulose Corp., Memphis, TN (Lot #9243BP)
3. Ruger Chemical Co., Irvington, NJ (Lot #861H101460)
4. Avicel PH101, FMC Corporation, Phila., PA (Lot #1530)
5. Cab-O-Sil, Cabot Corp., Boston, MA
6. Ruger Chemical Co., Irvington, NJ (Lot #F-1-0562)
7. Amend Drug & Chemical Co., Irvington, NJ (Lot #15949R24)
8. Courtesy of Premo Pharmaceutical Co., (Lot #C18283)

Cab-O-Sil		0.25%
Avicel PH 101	ad	100%
Hydrochlorothiazide		25%
Stearic acid		2%
Disintegrant		0, ¼, ½, 1 or 2%
Cab-O-Sil		0.25%
Avicel PH101	ad	100%

All formulations were mixed in a rotating shaker/mixer[9] for ten minutes. Tablet compaction was achieved using a rotary tablet press[10], keeping the press settings constant for all formulations of the same drug. The press was run at a speed of 30 r.p.m. for all formulations. The tablets were then tested for weight[11], harness[12], friability[13], tablet disintegration[14] and drug dissolution, using an automated sampling system[15] coupled with an ultraviolet spectrophotometer[16].

Results and Discussion

Figures 1 and 2 show the tablet properties of both sets of formulations. Figures 3 thru 9 show the disintegration and dissolution data.

For any given formulation tablet weight variation was less than ± 2%. The tablet hardness values (Erweka, kg) of all systems remained within two kilograms of the mean value. In general, hardness appears to be independent of disintegrant concentration. However, as

9. WAB Mixer, Turbula Model, Wiley A. Bachoven Co., Switzerland
10. Stokes Model B2, 16 station tablet press, Stokes-Penwalt Co.
11. Mettler Model H10 Balance, Mettler-Will Scientific, Rochester, NY
12. Erweka, Erweka Apperatabau, West Germany
13. Roche Friabilator, Erweka, West Germany
14. U.S.P. Apparatus with discs
15. Dissograph, Hanson Instruments Co., CA
16. Perkin-Elmer Hitachi 2000 Spectrophotometer

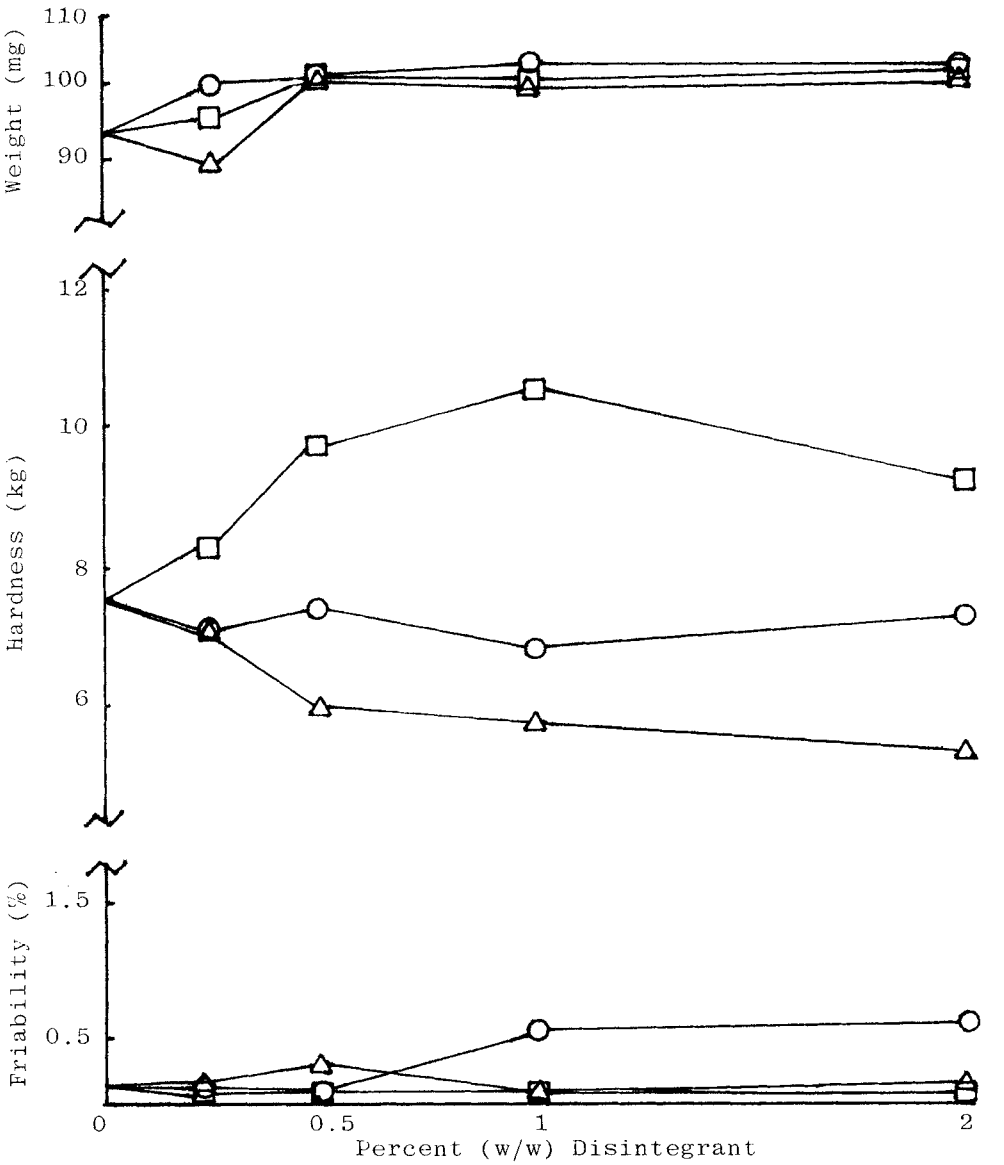

Fig. 1-Tablet Weight, Hardness and Friability of the Pyridoxine Formulations.

□-Corn Starch ○-Ac-Di-Sol △-CLD-2

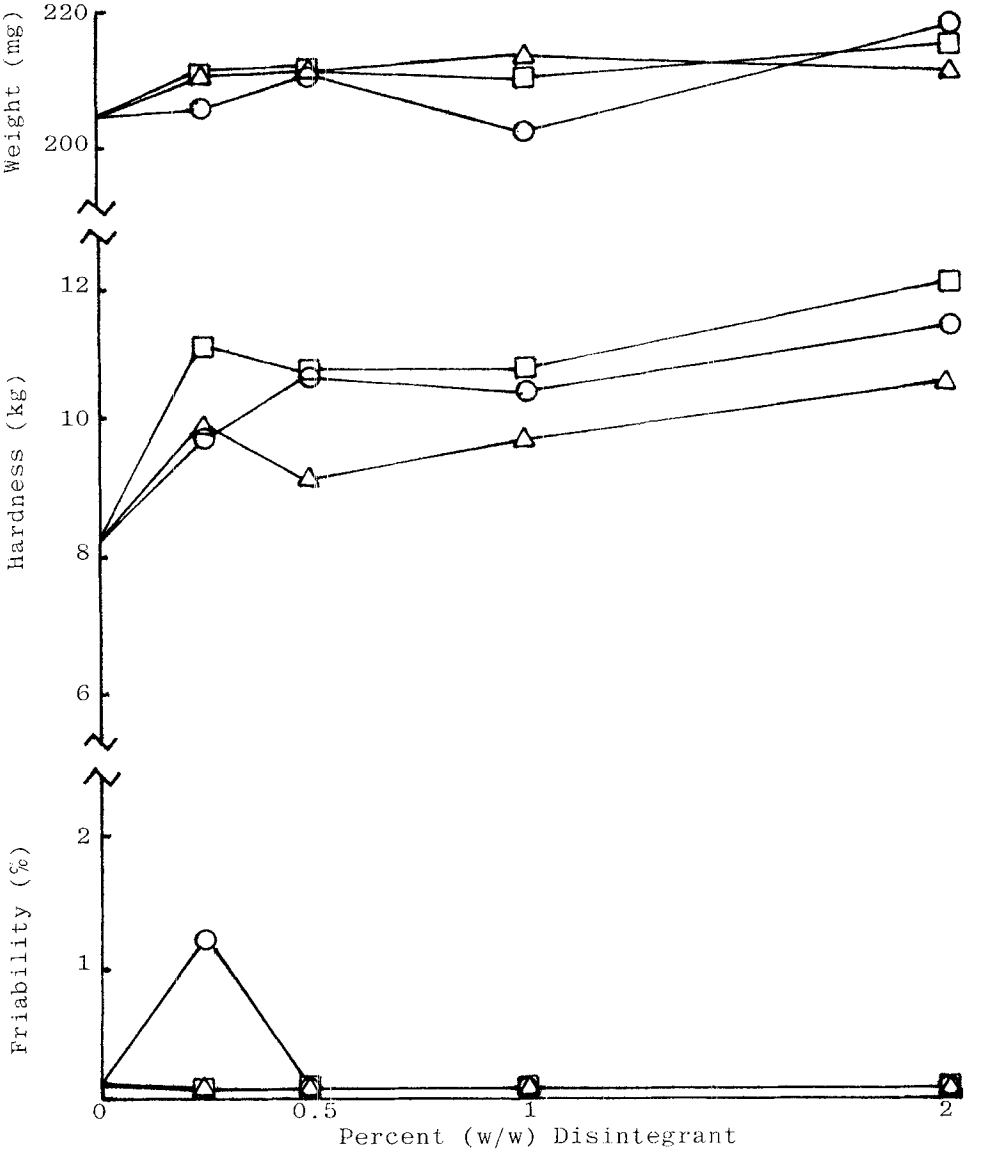

Fig. 2-Tablet Weight, Hardness and Friability of the Hydrochlorothiazide Formulations.

□-Corn Starch ○-Ac-Di-Sol △-CLD-2

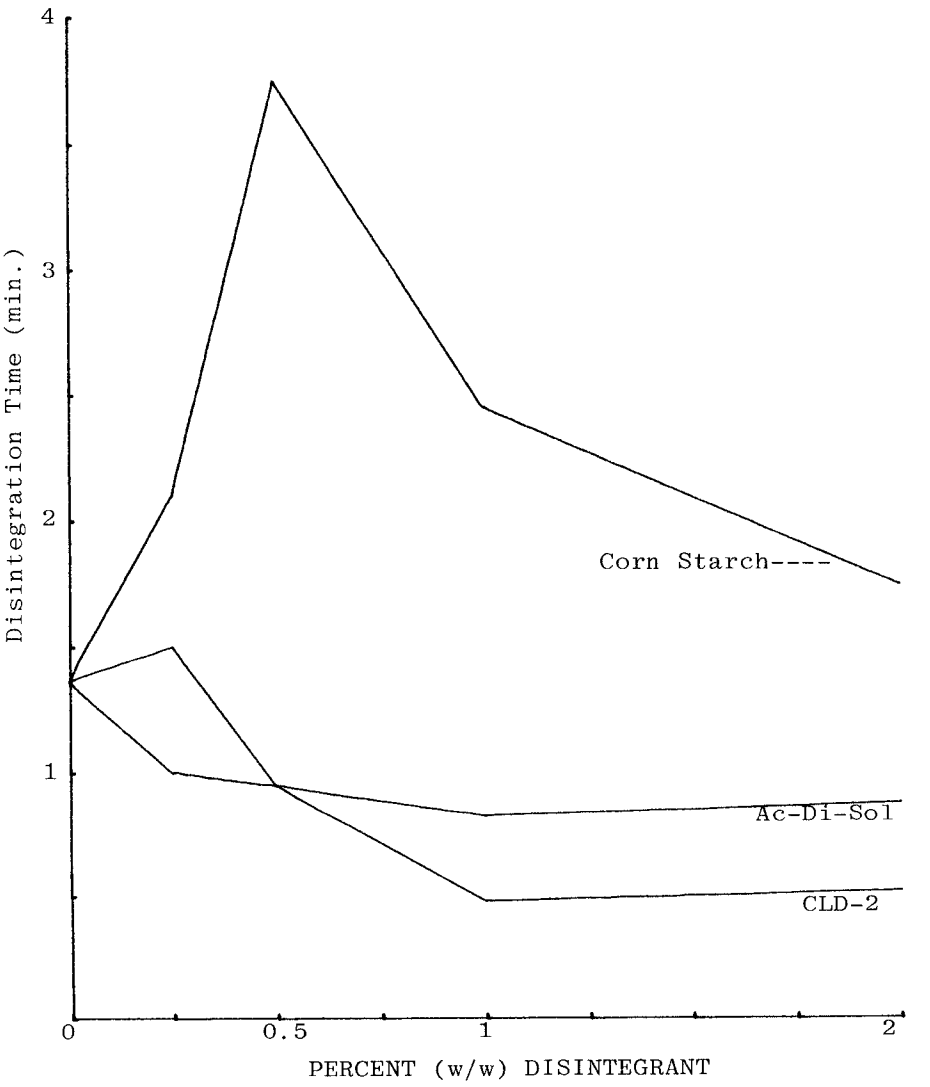

Fig. 3-Disintegration times of 3 disintegrants in a Pyridoxine formulation

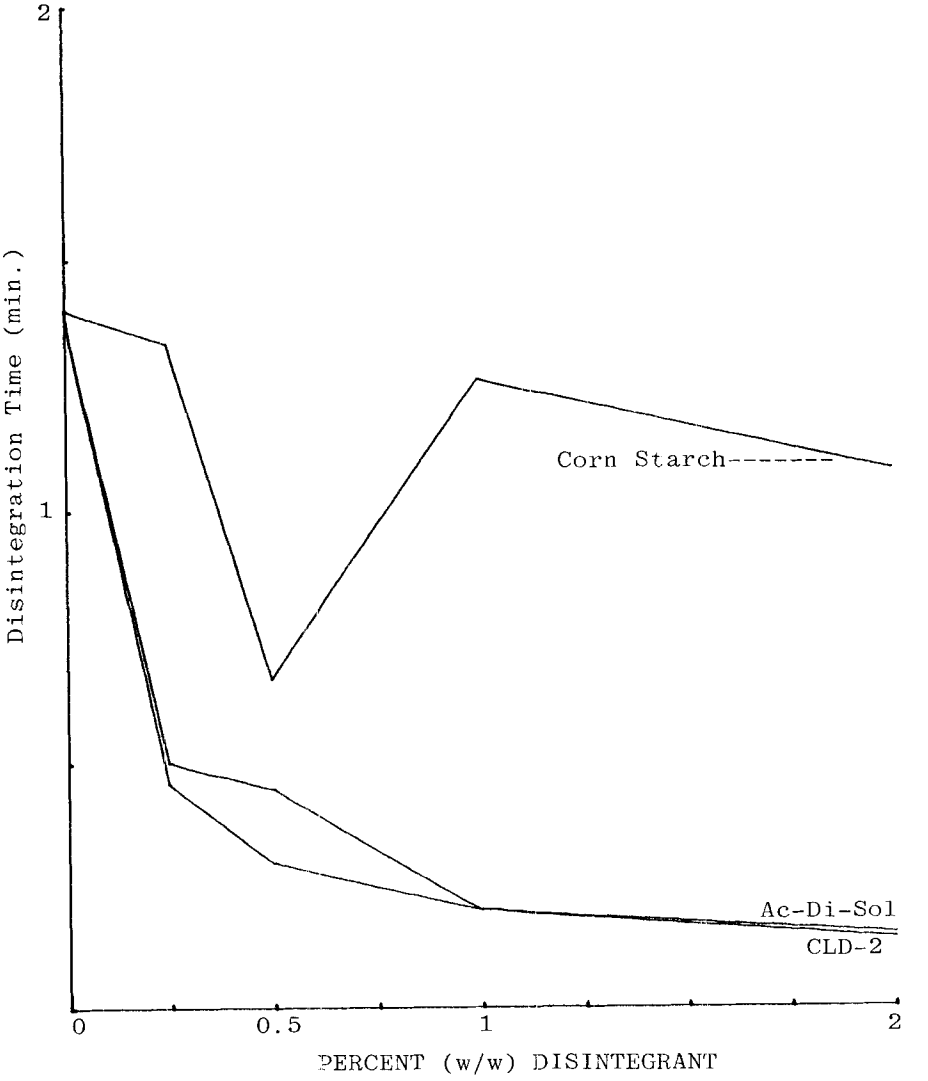

Fig. 4-Disintegration times of 3 disintegrants in a Hydrochlorothiazide formulation.

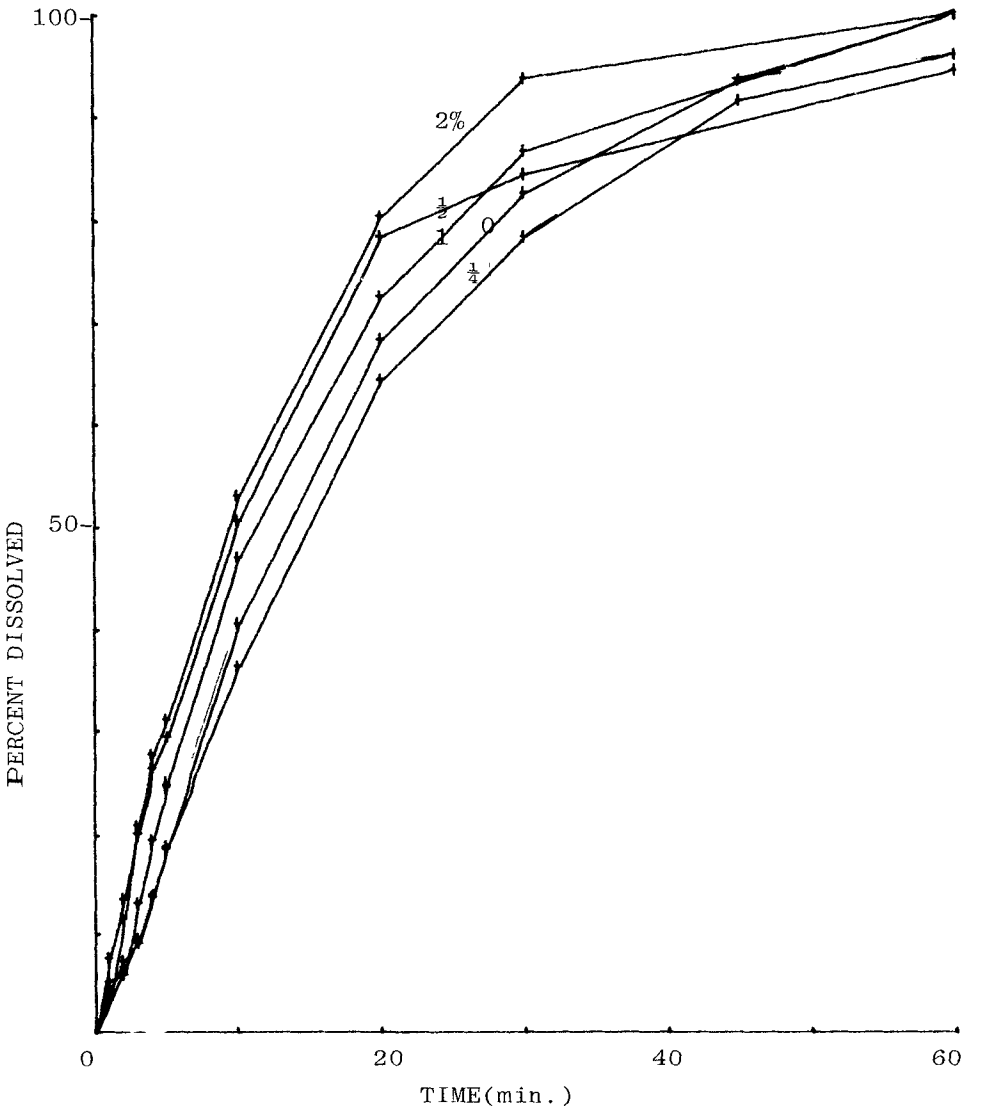

Fig. 5-Dissolution Curves for Pyridoxine/Corn Starch Formulation

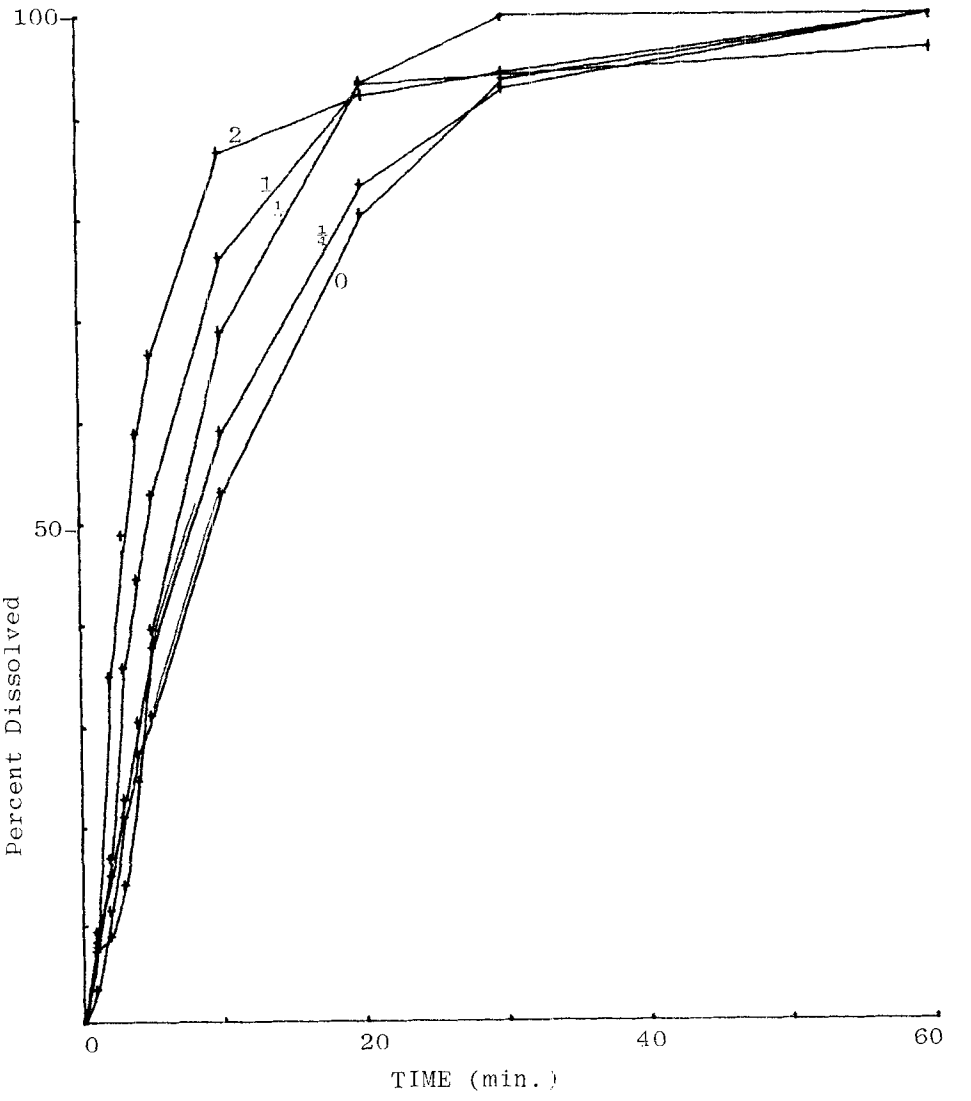

Fig. 6 -Dissolution Curves for Pyridoxine/Ac-Di-Sol Formulation

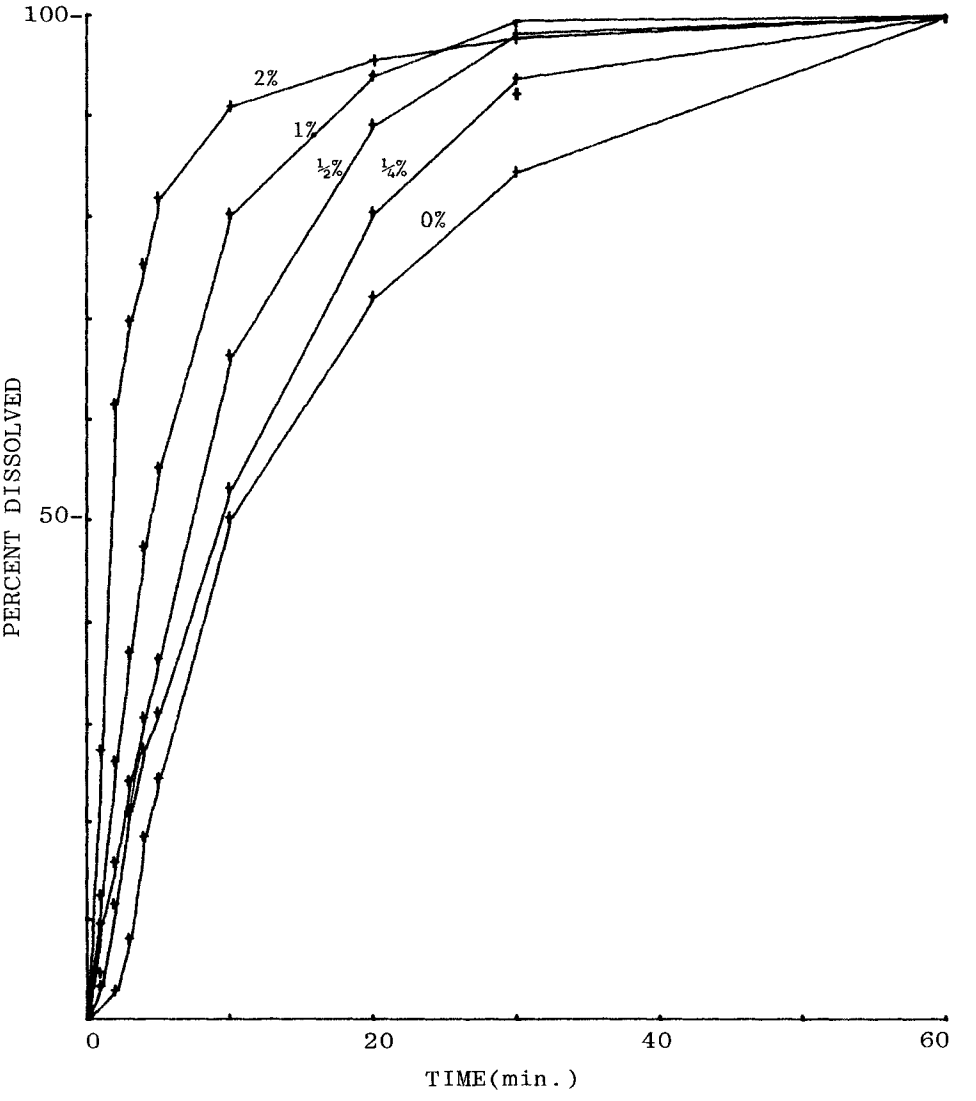

Fig. 7-Dissolution Curves for Pyridoxine/CLD-2 Formulation

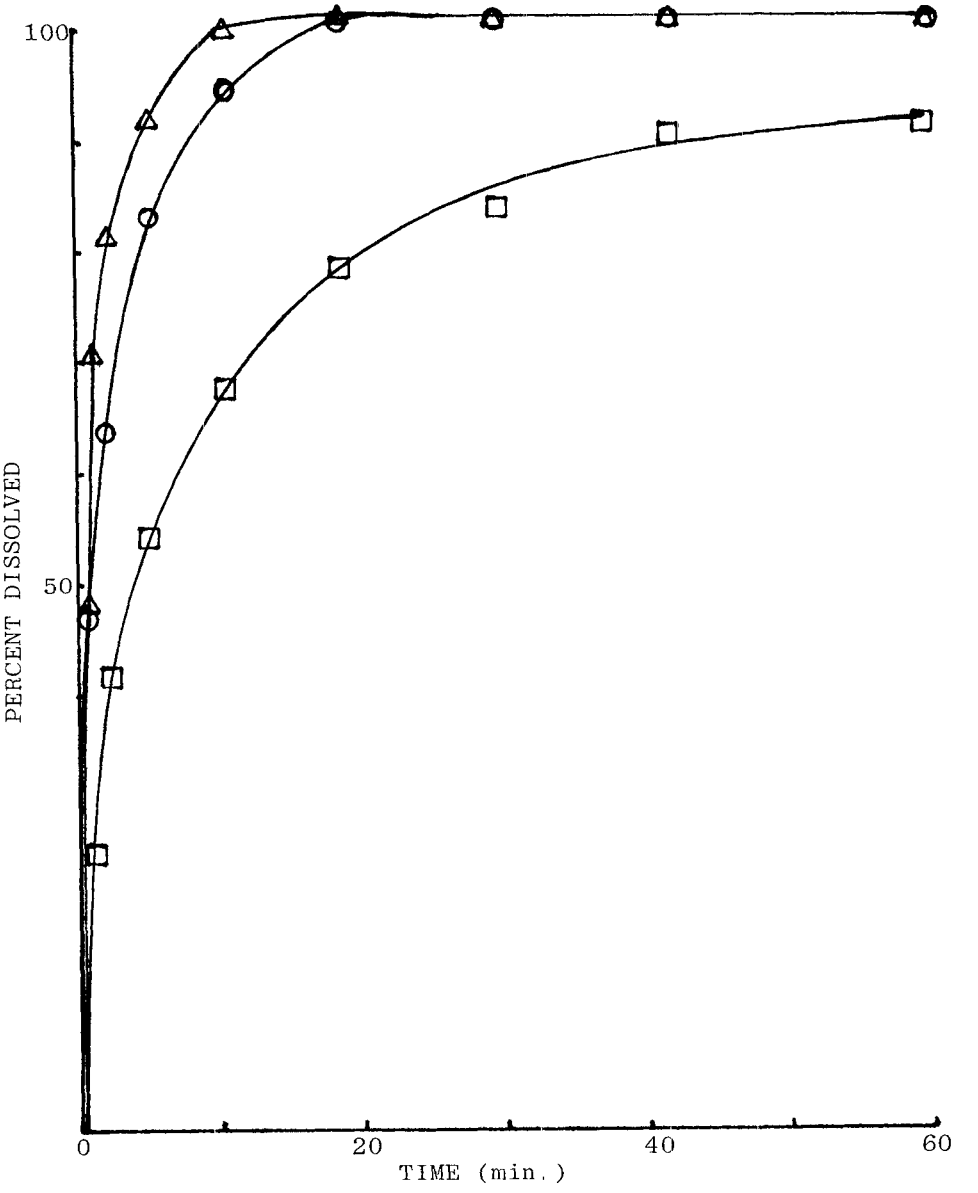

Fig. 8-Hydrochlorthiazide Formulations with 2% Disintegrant Dissolution Curves.

□-Corn Starch ○-Ac-Di-Sol △-CLD-2

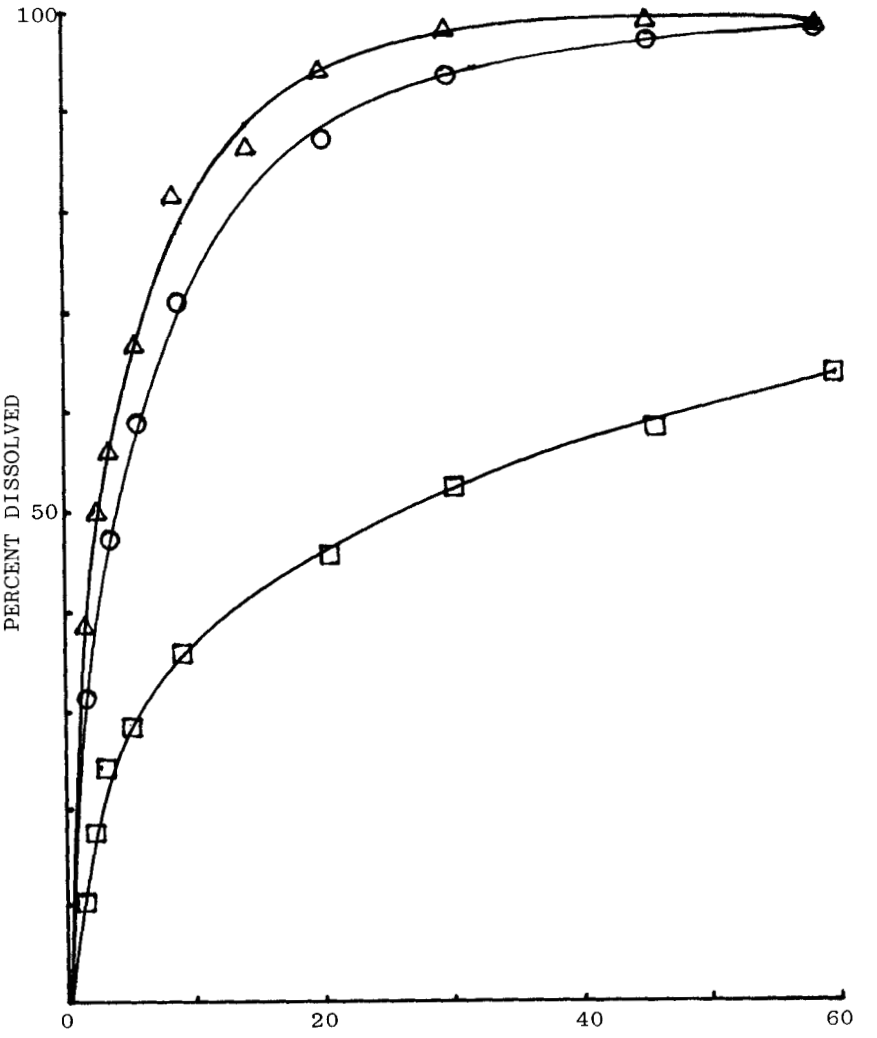

Fig. 9- Hydrochlorthiazide Formulations with ½% Disintegrant Dissolution Curves.

□-Corn Starch ○-Ac-Di-Sol △-CLD-2

disintegrant concentration increased in the pyridoxine formulation, the results varied. Tablets made with corn starch as disintegrant showed an increase in hardness for the lower concentrations. Hardness gradually decreased as the concentration approached two percent. This may possibly be due to a case-hardening effect, although this seems unlikely as the tablets were tested within a reasonable time after being tableted. The Ac-Di-Sol tablets showed essentially no change in tablet hardness for the pyridoxine formulation as concentration of disintegrant increased. Tablets made with CLD-2 show a slight reduction in hardness as disintegrant increased, but this effect was too small to be of practical importance. For the hydrochlorothiazide formulations, there appears to be a general trend for tablet hardness to increase as disintegrant concentration increased for all three tablet disintegrants.

The friabilities of the tablets for all formulations were well below two percent, although the highest friability was observed with the Ac-Di-Sol tablets. (Although there is no universal agreement on an upper acceptable limit for friability, the authors feel that values of less than 1% are desirable.)

In general, the disintegration times of each system appeared to parallel the hardness values. Both CLD-2 and Ac-Di-Sol disintegrants are markedly superior to corn starch.

The dissolution data for the pyridoxine formulations is shown in Fig.'s 4 thru 6. Even at the 2% level, corn starch gave a T_{90} (time for ninety per cent of drug to dissolve) of about thirty minutes. By contrast, both CLD-2 and Ac-Di-Sol were very much more effective in causing dissolution (T_{90} at 2% about 16 minutes for Ac-Di-Sol and about 10 minutes for CLD-2). For both Ac-Di-Sol and CLD-2 it is apparent that formulations with very rapid dissolution can be obtained with quite low concentrations of disintegrants.

As might be expected, the differences in disintegrant efficiency are more substantial in the hydrochlorothiazide formulations. The aqueous solubility of hydrochlorothiazide is much lower than that of pyridoxine. Indeed, there is indication that some workers consider hydrochlorothiazide to be a model drug of particular value

for the evaluation of disintegrant efficiency. The present authors are by no means certain that any one drug can fill the model role. However, we do feel that this drug is indeed a useful substance for dissolution studies.

The data shown in Fig.'s 8 and 9 demonstrates that even at the 2% level corn starch is of questionable value as a disintegrant in the hydrochlorothiazide formulations. The T_{90} values for the three disintegrants at the 2% level are about 5 minutes for CLD-2, 10 minutes for Ac-Di-Sol and over 50 minutes for corn starch. At the 0.5% level T_{90} values are about 8 minutes for CLD-2, 18 minutes for Ac-Di-Sol and more than 60 minutes for corn starch.

The dissolution data reported in this study supports the contention that with the modern so-called "super disintegrants" formulators may well find levels of 1% or less may be sufficiently effective in some systems (2).

The data presented in this paper abundantly demonstrates that CLD-2 is a powerful disintegrant which gives hard tablets of low friability, good weight uniformity and very rapid disintegration and dissolution profiles. Its performance is at least as good as, and possibly better than, that of Ac-Di-Sol. Obviously, both CLD-2 and and Ac-Di-Sol are very significantly superior to corn starch.

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