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STUDIES OF THE UTILITY OF CROSS LINKED POLYVINYLPOLYPYRROLIDINE AS A TABLET DISINTEGRANT

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ABSTRACT

Studies of different particle size grades of cross linked polyvinylpolypyrrolidone (Polyplasdone G.A.F. Corporation) in direct compression tablet formulations show that increase in mean particle size enhances powder flow, disintegration and dissolution although hardness and friability were slightly better for tablets made from the finer grades. The disintegrant exhibits powerful disintegrant action at low concentrations. It should probably be rarely, if ever, necessary to use more than five per cent in a tablet in order to achieve rapid dissolution. It appears that the use of polyvinylpolypyrrolidone (P.V.P.P.) as a tablet disintegrant at high concentrations may be self limiting since certain properties such as powder flow, tablet weight variation, hardness and friability start to reach unacceptable levels at high disintegrant concen-

trations. Data presented in this paper indicates that tablets containing acetylsalicylic acid or multi-vitamins can be very effectively formulated using P.V.P.P. as a disintegrant.

INTRODUCTION

Several investigators have studied the use of Polyvinylpolypyrrolidone (P.V.P.P.) in pharmaceutical systems as a disintegrant (1-6). Huttenrauch and Keiner in 1973 (3) showed P.V.P.P. to be superior to other standard disintegrants. Kornblum and Stoopak (5) compared physical properties of P.V.P.P. with other disintegrants in order to differentiate disintegration efficiency. These investigators also pointed out that P.V.P.P. can be easily incorporated into direct compression systems and that the wet granulation technique does not interfere with the desired tablet disintegration properties. Similar properties were also reported by Khan and Rooke (4).

The connection between disintegration and dissolution of systems containing P.V.P.P. has also been investigated by Kornblum and Stoopak using 25 mg. of isoquinazoline compound in both direct compression and wet granulation systems.

Amussen et al (1) and Kwee and Ulex (6) studied the dissolution of pharmaceutical systems containing digoxin using P.V.P.P. as a disintegrant. These investigators showed that dissolution reproducibility is remarkable for these systems.

Flasch et al (2) showed that it was possible to produce digoxin tablets with a bioavailability of 82%. These tablets reached the same high level in bioavailability as an aqueous/alcoholic digoxin solution.

Following these studies, it was obvious that P.V.P.P. had tremendous promise in pharmaceutical systems as a disintegrant. Therefore, efforts were taken to try to optimize disintegrant func-

tion. Since neither the effect of particle size on disintegrant efficiency nor dissolution efficiency has been extensively explored, it was considered important to do so.

EXPERIMENTAL

MATERIALS - Polyvinylpolypyrrolidone in three particle size ranges: 0-15 microns (Grade A)[1], 50-100 microns (Grade B)[2] and 50-300 microns (Grade C)[3], Dibasic Calcium Phosphate Dihydrate[4], Microcrystalline Cellulose in two particle size ranges[5,6] Aspirin[7], Magnesium Stearate, Riboflavin[8], Pyridoxine[8], Niacin[9], Ascorbic Acid[9].

FLOW EVALUATION - A recording powder "flow-meter" (7, 8) was constructed, consisting of a large funnel suspended over a balance/recording mechanism. A stainless steel hopper, from a Stokes Model F, single punch press, was used as the funnel. The recording device consisted of two pieces: (1) an analog-balance[10] which sends electrical output to (2) a strip-chart recorder[11]. The recorder was calibrated such that 1 Kg. weight on the pan would cause a pen deflect on equal to the entire chart scale. The chart speed was set at 30 cm./min. throughout the study.

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[1]Agent AT-888, GAF Corporation

[2]Polyplasdone XL 499 Special, GAF Corporation

[3]Polyplasdone XL, GAF Corporation

[4]Emcompress, Edward Mendell Co.

[5]Avicel PH 101 FMC Corporation

[6]Avicel PH 102, FMC Corporation

[7]Ruger Chemical

[8]Nutritional Biochemicals

[9]J. T. Baker Chemical Co.

[10]Sartorius

[11]Single Pen Model, Lingar Inc.

METHODS - The study was separated into two phases. In phase I, three different particle size ranges of Polyvinylpolypyrrolidone (PVPP) were selected. Using the analog-balance flowmeter described earlier, the three grades of PVPP in a 2% (w/w) concentration, in three different excipients, mass flow/time and linearity was determined for 1 Kg. of each of the nine systems. Mixing of all systems was carried out in a stainless steel twin shell blender[12] over a period of five minutes. This procedure was constant throughout the study. The three excipients (Dibasic Calcium Phosphate Dihydrate[4], Microcrystalline Cellulose in two particle size ranges [5,6]) were selected for their range of flow properties.

Using a rotary press[13] at a speed of approximately 600 tablets/minute, the various grades of P.V.P.P. and excipients were tableted according to the following formulation:

Aspirin	30.0% (w/w)
P.V.P.P. (A, B, or C)	2.0% (w/w)
Mag. Stearate	0.5% (w/w)
Excipient ad	100 %

Tablet weight was evaluated[14] and R.S.D. (relative standard deviation) values are given as a measure of weight variation. Hardness[15] is in Kg. units. Friability was determined in standard fashion[16] and is reported as percentage tablet weight. Both disintegration and dissolution were carried out on U.S.P. apparatus with all procedures being standard. Thickness was evaluated using a micrometer[17].

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[12] Patterson-Kelley Co.

[13] Colton Model 216

[14] Mettler Model H8

[15] Erweka Hardness Tester

[16] n = 20, t = 20 min.

[17] Zeus

In the second phase, one particle size grade was selected using the data generated, and again tests were run. Flow was evaluated by the previously stated methods. The concentration of P.V.P.P. was varied from 0-20% (w/w) in 1 Kg. of excipient.

Using a rotary press[13], the selected grade (C) was incorporated in concentrations of 0, 1, 2, 5, 10 and 20% (w/w) in a multivitamin formulation listed below:

Riboflavin (B_2)	0.7%
Pyridoxine (B_6)	1.0%
Niacin	7.0%
Ascorbic Acid (C)	20.0
Mag. Stearate	0.5%
Polyplasdone XL (Grade C)	X%
Emcompress ad	100 %

Tablets were tested using the previously described methods for weight, thickness, hardness, friability, and disintegration.

Finally, a concentration was selected for Grade C and was incorporated into a single entity formulation listed below.

Pyridoxine (B_6)	5%
Polyplasdone XL	2%
Mag. Stearate	0.5%
Emcompress ad	100 %

Tablets were tested using the previously described methods for weight, thickness, hardness, friability, disintegration and dissolution. Content uniformity of 30 tablets was also evaluated.

RESULTS AND DISCUSSION

Tables Ia-Ic list the flow properties of the three grades of P.V.P.P. in three different excipients. For each excipient, the trend seems to be the same. As particle size of P.V.P.P. increases, flow tends to improve. With the slower-flowing matrices (Microcrystalline Celluloses), this trend is only just discernable, but can readily be seen with the faster-flowing Dibasic Calcium Phosphate Dihydrate.

Tables II-VII (a-c) list tablet data for the Aspirin formulation described earlier (30% A.S.A., 2% P.V.P.P.).

Table Ia - FLOW PROPERTIES OF EMCOMPRESS WITH 2% P.V.P.P.
(Various Grades)

GRADE	MEAN[1] MASS FLOW (Gm/Sec)	MEAN[2] LINEARITY[2]
A	163	17.9
B	194	18.8
C	224	18.4

[1] n = 3
[2] Linearity = $(r^2 - 0.8) \times 100$

Table Ib - FLOW PROPERTIES OF AVIDEL PH 101 WITH 2% P.V.P.P.
(Various Grades)

GRADE	MEAN[1] MASS FLOW (Gm/Sec)	MEAN[2] LINEARITY[2]
A	22	18.1
B	22	18.4
C	24	19.1

[1] n = 3
[2] Linearity = $(r^2 - 0.8) \times 100$

Table Ic - FLOW PROPERTIES OF AVICEL PH 102 WITH 2% P.V.P.P.
(Various Grades)

GRADE	MEAN[1] MASS FLOW (Gm/Sec)	MEAN[2] LINEARITY[2]
A	29	17.7
B	29	17.9
C	30	18.6

[1] n = 3
[2] Linearity = $(r^2 - 0.8) \times 100$

Table IIa - 30% ACETYLSALICYLIC ACID AND 2% P.V.P.P. WITH EMCOMPRESS AS A MATRIX

	TABLET WEIGHT	
	MEAN TABLET WEIGHT	R.S.D.
GRADE A	403.2	0.99
GRADE B	382.3	0.93
GRADE C	376.7	1.24

Table IIb - 30% ACETYLSALICYLIC ACID AND 2% P.V.P.P. WITH AVICEL 101 AS A MATRIX

	TABLET WEIGHT	
	MEAN TABLET WEIGHT	R.S.D.
GRADE A	276.3	1.88
GRADE B	184.9	1.40
GRADE C	292	0.51

Table IIc - 30% ACETYLSALICYLIC ACID AND 2% P.V.P.P. WITH AVICEL 102 AS A MATRIX

	TABLET WEIGHT	
	MEAN TABLET WEIGHT	R.S.D.
GRADE A	294.8	1.33
GRADE B	195.4	1.90
GRADE C	306.3	0.83

Table IIIa - 30% ACETYLSALICYLIC ACID AND 2% P.V.P.P. WITH EMCOMPRESS AS A MATRIX

	TABLET HARDNESS	
	MEAN TABLET HARDNESS	R.S.D.
GRADE A	5.8	8.11
GRADE B	5.3	15.53
GRADE C	4.8	14.06

Table IIIb - 30% ACETYLSALICYLIC ACID AND 2% P.V.P.P. WITH AVICEL 101 AS A MATRIX

	TABLET THICKNESS	
	MEAN TABLET THICKNESS (mm)	R.S.D.
GRADE A	3.83	1.64
GRADE B	3.97	0.81
GRADE C	4.04	0.67

Table IIIc - 30% ACETYLSALICYLIC ACID AND 2% P.V.P.P. WITH AVICEL 102 AS A MATRIX

	TABLET THICKNESS	
	MEAN TABLET THICKNESS (mm)	R.S.D.
GRADE A	4.04	0.76
GRADE B	4.06	1.62
GRADE C	4.17	0.86

Table IVa - 30% ACETYLSALICYLIC ACID AND 2% P.V.P.P. WITH EMCOMPRESS AS A MATRIX

	TABLET THICKNESS	
	MEAN TABLET THICKNESS (mm)	R.S.D.
GRADE A	4.32	0.64
GRADE B	4.30	0.49
GRADE C	4.18	0.64

Table IVb - 30% ACETYLSALICYLIC ACID and 2% P.V.P.P. WITH AVICEL 101 AS A MATRIX

	TABLET HARDNESS	
	MEAN TABLET HARDNESS (Kg)	R.S.D.
GRADE A	8.6	13.65
GRADE B	6.8	20.44
GRADE C	6.4	9.86

Table IVc - 30% ACETYLSALICYLIC ACID AND 2% P.V.P.P. WITH AVICEL 102 AS A MATRIX

	TABLET HARDNESS	
	MEAN TABLET HARDNESS	R.S.D.
GRADE A	6.5	14.36
GRADE B	6.3	12.65
GRADE C	6.0	6.87

Table Va - 30% ACETYLSALICYLIC ACID AND 2% R.V.P.P. WITH EMCOMPRESS AS A MATRIX

	TABLET DISINTEGRATION	
	MEAN DISINTEGRATION TIME	RANGE
GRADE A	71	45-79
GRADE B	58	30-70
GRADE C	34	30-40

Table Vb - 30% ACETYLSALICYLIC ACID AND 2% P.V.P.P. WITH AVICEL 101 AS A MATRIX

	TABLET DISINTEGRATION	
	MEAN TABLET DISINTEGRATION (sec)	RANGE
GRADE A	47	30-70
GRADE B	33	25-40
GRADE C	46	30-60

Table Vc - 30% ACETYLSALICYLIC ACID AND 2% P.V.P.P. WITH AVICEL 102 AS A MATRIX

	TABLET DISINTEGRATION	
	MEAN TABLET DISINTEGRATION (sec)	RANGE
GRADE A	47	40-55
GRADE B	47	40-55
GRADE C	44	43-46

Table VIa - 30% ACETYLSALICYLIC ACID AND 2% P.V.P.P. WITH EMCOMPRESS AS A MATRIX

TABLET FRIABILITY	
GRADE	% FRIABILITY
A	0.70
B	0.77
C	0.94

Table VIb - 30% ACETYLSALICYLIC ACID AND 2% P.V.P.P. WITH AVICEL 101 AS A MATRIX

TABLET FRIABILITY	
GRADE	% FRIABILITY
A	0.40
B	0.63
C	0.69

Table VIc - 30% ACETYLSALICYLIC ACID AND 2% R.V.P.P. WITH AVICEL 102 AS A MATRIX

TABLET FRIABILITY	
GRADE	% FRIABILITY
A	0.17
B	0.27
C	0.41

Table VII - MULTIVITAMIN TABLET WEIGHT

% P.V.P.P. (Grade C)	MEAN TABLET WEIGHT (mg)	R.S.D.
0	237.4	0.77
1	160.0	1.44
2	219.8	1.90
5	206.3	0.89
10	180.3	1.23
20	162.7	2.47

Tables IIa-IIc list the tablet weight and Relative Standard Deviation (R.S.D.) values for the matrices and grades of P.V.P.P. In all cases, R.S.D. values are well within acceptable limits and changes in tablet weights can probably be attributed to differing densities of the P.V.P.P. grades and the matrices. With the more dense matrix (Dibasic Calcium Phosphate Dihydrate), there is a trend to decrease tablet weight given the same die-fill as P.V.P.P. particle size increases. With the less-dense Microcrystalline Celluloses, this trend seems to be reversed.

Tables IIIa-IIIc list the Erweka tablet hardness and R.S.D. values for the matrices and grades. In all three matrices, the trend is noticeable. As particle size increases, hardness tends to decrease, although this change is not very dramatic. All R.S.D. values for hardness are within normal limits.

Tables IVa-c list values for tablet thickness and R.S.D. values for the grades of P.V.P.P. and excipients. These values reflect those in tables IIa-IIc (weight) and can be attributed to these differences.

Tables Va-Vc list percentage friability for the various systems. Although there is a slight trend showing an increase in the amount of compact lost due to abrasion as the particle size increases, this is only a slight trend and all values are within acceptable limits.

Tables VIa-VIc list the disintegration times of the tablets and the time range. In almost all cases, the disintegration time was below one minute, and, this is, of course, most satisfactory. However, out of the three grades, grade C, with the largest particle size, gives the fastest disintegration.

Figures I-III show the dissolution curves of the three grades of P.V.P.P. for the three excipients. In all cases, as particle size increases and becomes broader, dissolution is enhanced.

Based on all the above observations, grade C (Polyplasdone XL) seems to be the best of the three grades tested.

Using the miltivitamin formulation described earlier, the percentage P.V.P.P. (Grade C) was increased progressively from zero to twenty. Table VII lists the tablet weights and R.S.D. values and it can be seen that tablet weight decreases as P.V.P.P. concentration increases. This most probably is due to differences in density and may be overcome by increasing the die-fill, but it must also be noted that the weight variation also increases with P.V.P.P. concentration, and this may be significant.

Table VIII lists tablet thickness and R.S.D. values. These differ only slightly at 10% P.V.P.P. or less and are not very significant.

Table IX lists the Erweka hardness of the tablets and R.S.D. values. There is quite a noticeable decrease in hardness as P.V.P.P. concentration increases. R.S.D. value are normally high for hardness.

Table X lists percentage friability of the tablets. The abrasion potential tends to increase with P.V.P.P. concentration, although at concentrations of 5% or less, it is within normal limits.

In Table XI, disintegration time and time ranges are listed. As expected, disintegration time decreases with increasing P.V.P.P. concentration. It seems that one percent P.V.P.P. has little effect on disintegration time of this formulation, while 2% seems optimum.

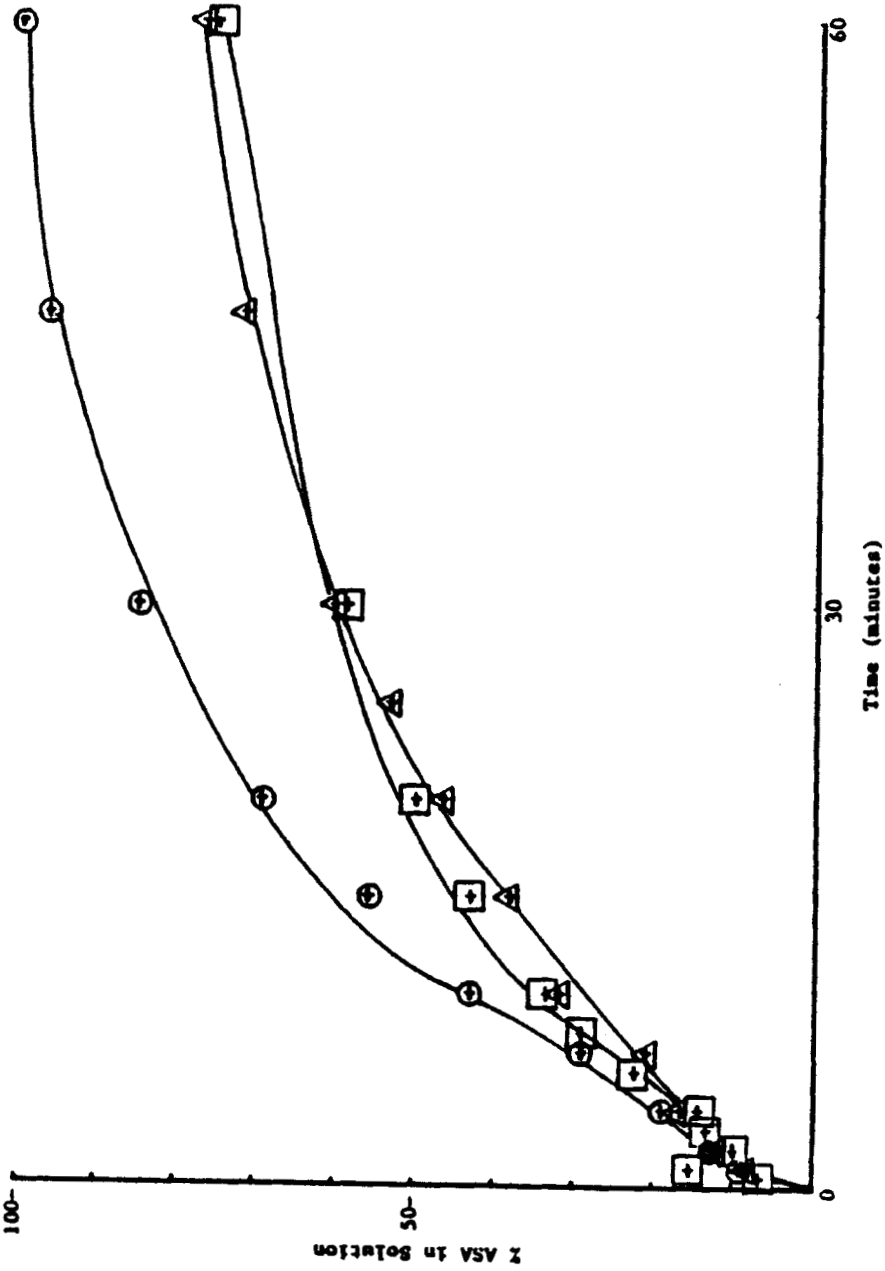

Fig. 1- ASA Formulation/Avicel PH102 Dissolution Curves
□-Grade A △-Grade B ○-Grade C)

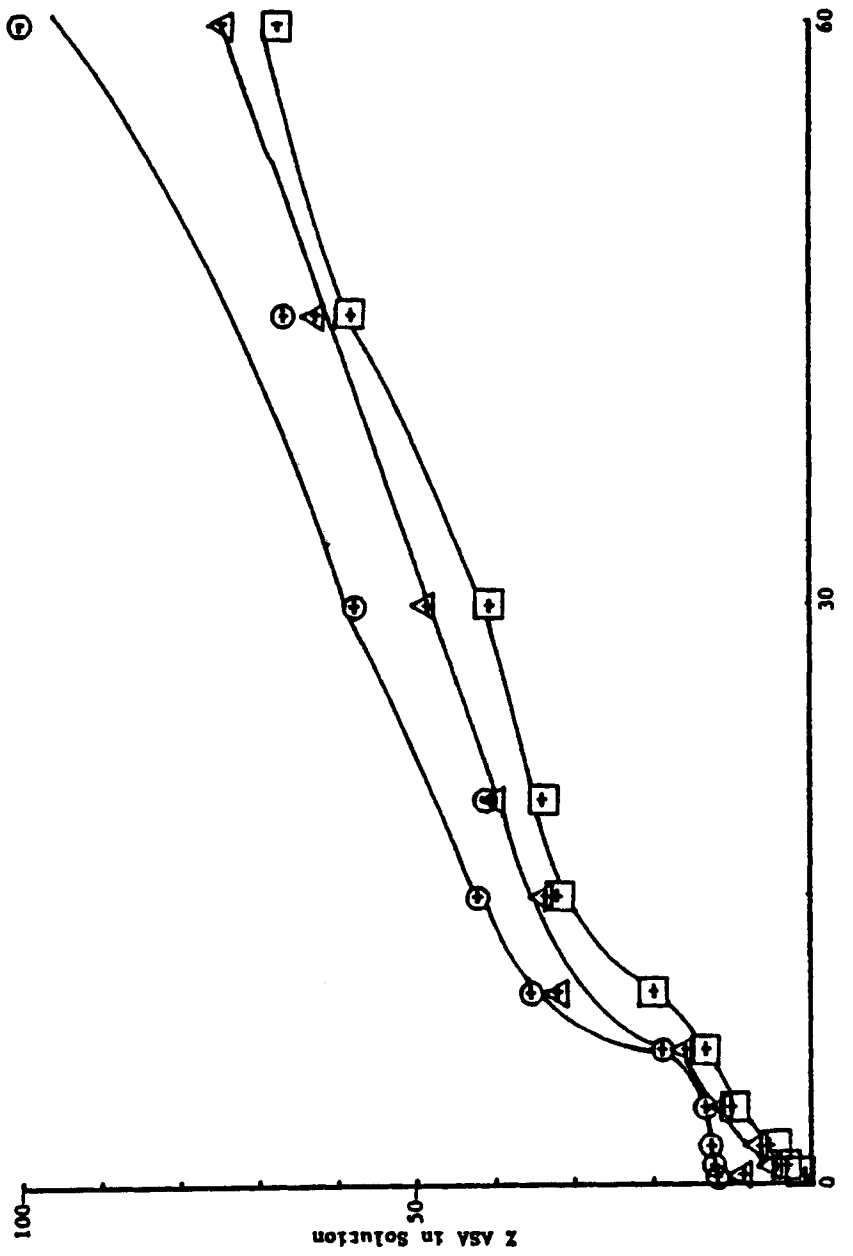

Fig. II- ASA Formulation/Avicel PH101 Dissolution Curves
(□-Grade A, △-Grade B, ○-Grade C)

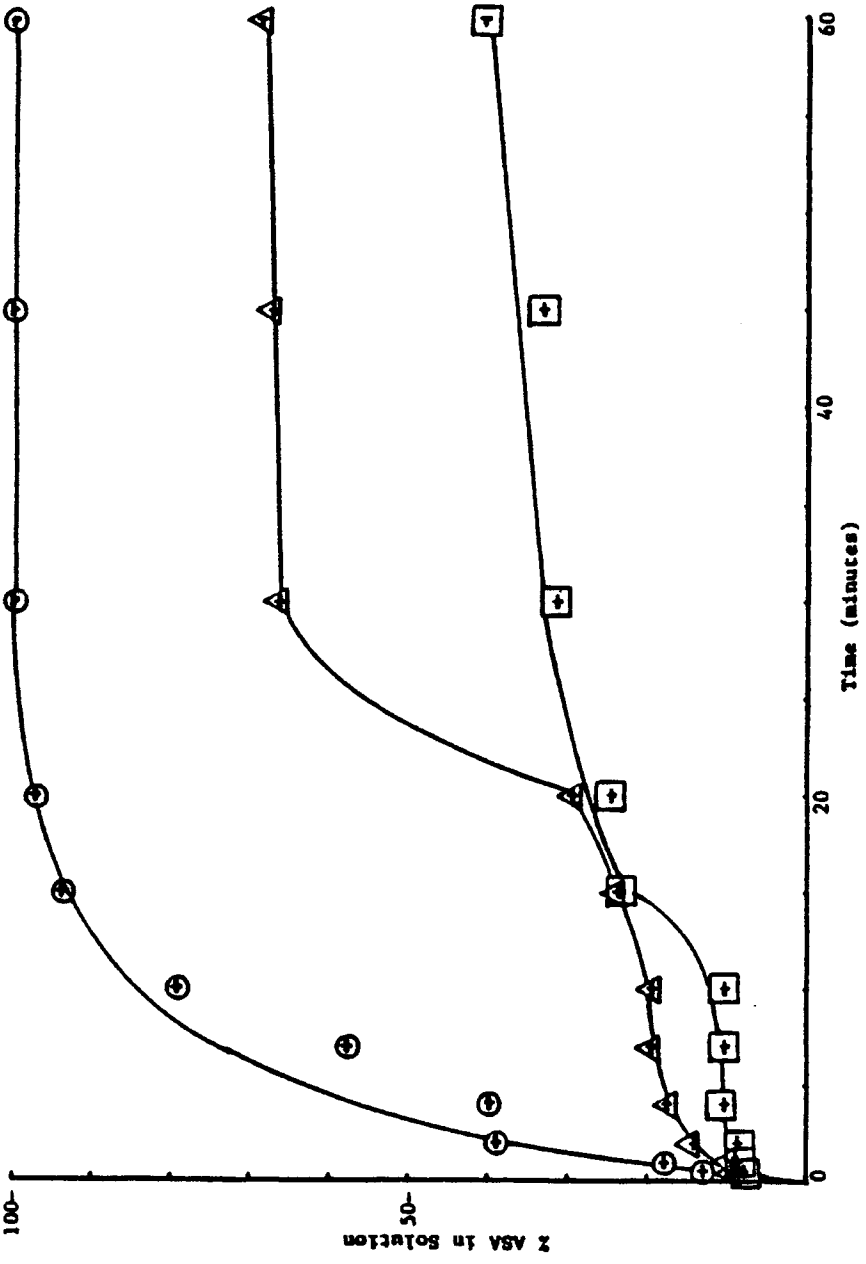

Fig. III- ASA Formulation/Encompress Dissolution Curves
Grade A, Grade B, Grade C

Table VIII - MULTIVITAMIN TABLET THICKNESS

% P.V.P.P. (Grade C)	MEAN TABLET THICKNESS (mm)	R.S.D.
0	4.92	0.25
1	5.17	0.43
2	4.85	0.30
5	4.86	0.34
10	4.95	0.45
20	5.31	0.71

Table IX - MULTIVITAMIN TABLET HARDNESS

% P.V.P.P. (Grade C)	MEAN TABLET HARDNESS (Kg)	R.S.D.
0	7.0	9.25
1	5.5	25.71
2	4.0	19.29
5	2.6	14.47
10	1.2	21.00
20	75	-

Table X - MULTIVITAMIN TABLET FRIABILITY

%P.V.P.P. (Grade C	% FRIABILITY
0	0.42
1	0.06
2	0.41
5	1.37
10	15.88
20	100.00

Table XI - MULTIVITAMIN TABLET DISINTEGRATION

% P.V.P.P. (Grade C)	MEAN DISINTEGRATION TIME	RANGE
0	245	200-300
1	236	210-270
2	26	20-30
5	5	2-10
10	3	1-5
20	2	0-3

Table XII - EFFECT OF INCREASING AMOUNTS OF P.V.P.P. (Grade C) ON FLOW PROPERTIES OF EMCOMPRESS

% P.V.P.P.	MEAN[1] FLOW RATE (Gm/Sec)	MEAN[1] LINEARITY (r^2 - 0.8) x 100
0	226.5	18.6
1	227.4	19.4
2	202.8	19.2
5	199.3	18.6
10	176.5	18.9
20	130.5	18.9

[1]Three trials

Table XIII - PYRIDOXINE (B_6) 5 mg TABLET DATA (P.V.P.P. (Grade C) 2%)

	MEAN	R.S.D.
WEIGHT	100.6 mg	1.66
THICKNESS	2.497 mm	0.84
DISINTEGRATION	8 sec	6-10 (range)
FRIABILITY	0.84%	-
CONTENT (ASSAYED)[1]	5.029 mg	0.02

[1]n = 30

Table XII lists flow characteristics of Dibasic Calcium Phosphate Dihydrate as P.V.P.P. concentration increases. The decrease in the mass flow rate can be seen readily on the fast-flowing matrix while the decrease in linearity is not as visible. This would most probably be evident on a slower flowing excipient.

From the above data, a concentration of two percent P.V.P.P. was selected as the best and was incorporated into a single-entity formulation (Pyridoxine) as described earlier. Table XIII lists the tablet data. Tablet weight thickness, and friability are well within acceptable limits, and content assayed is extremely uniform for 30 tablets.

In conclusion, the work reported in this study indicates that, as the particle size of Polyvinylpolypyrrolidone (P.V.P.P.) is increased, disintegrant activity, dissolution, and flow properties are enhanced.

In addition, it seems likely that P.V.P.P. (in a particle size range of 50-300 microns) will be useful as a tablet disintegrant at levels of 1-5% for most systems. Although further work is needed to expand on many of the concepts introduced in this report, this study clearly indicates that P.V.P.P. has considerable potential for use as a pharmaceutical disintegrant.

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