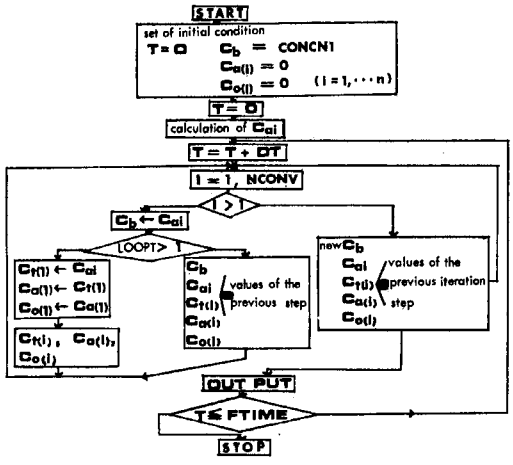
local continuous phase, and (*b*) the extent to which the internal phase acts as a pathway for transport of the solute. The theoretical procedure permits the calculation of the influences of the interfacial barrier permeability coefficient, the particle size, the volume fractions of the phases, and the partition coefficients in the phases upon the solute transport rates through the heterogeneous media.

APPENDIX: NUMERICAL COMPUTATION PROCEDURE

The flow diagram of the calculating procedure is briefly shown in Scheme I. After $t = 0$, a series of calculation procedures undergo



Scheme I—Flow diagram for computation of concentration distributions

successive approximation for each time increment, Δt. On the calculation of C_b, $C_{t(i)}$, $C_{a(i)}$, and then $C_{o(i)}$ at $t = \Delta t$, the first approximation of ΔC_b is obtained from Eq. 1, assuming $(C_{ai})_{t=\Delta t} = (C_{ai})_{t=0}$. Then under the assumption of both $C_{a(i)}$ and $C_{a(i+1)} = 0$, the first approximation of $\Delta C_{t(i)}$ is calculated by Eqs. 4, 6, and 8, respectively, and then $C_{t(i)}$ at $t = \Delta t$ is assumed $\Delta C_{t(i)}$ for $0 < t \leqq \Delta t$. Next, by assuming $\Delta C_{o(i)} = 0$, $\Delta C_{t(i)} = \Delta C_{a(i)}$ according to Eq. 3 and then $C_{a(i)}$ is also assumed $0.5 \times \Delta C_{a(i)}$ for $0 < t \leqq \Delta t$. Accordingly, $\Delta C_{o(i)}$ is calculated by Eqs. 5, 7, and 9, respectively, under the assumption of $C_{o(i)} = 0$, and then $C_{o(i)}$ is assumed $0.5 \times \Delta C_{o(i)}$ for $0 < t \leqq \Delta t$. The second approximations of C_{ai}, C_b, $C_{t(i)}$, $C_{a(i)}$, and $C_{o(i)}$ are calculated by using the first approximations successively. These procedures are repeated until respective values converge. The calculation of the next step (added Δt) starts from the values of one step before in the same manner mentioned above.

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▲ To whom inquiries should be directed.

A New Tablet Disintegrating Agent: Cross-Linked Polyvinylpyrrolidone

SAUL S. KORNBLUM▲ and SAMUEL B. STOOPAK

Abstract □ Cross-linked polyvinylpyrrolidone was studied for its disintegration property in comparison to starch USP and alginic acid. Certain physical parameters of the disintegrants (maximum moisture sorption, hydration capacity, bulk density, and specific surface area) were determined for the purpose of differentiating their relative efficiency. A linear relationship was found to exist when the maximum moisture sorption was plotted *versus* the specific surface area for each disintegrant. It was postulated that capillary activity of the cross-linked polyvinylpyrrolidone for water appears responsible for its tablet disintegration property. Cross-linked polyvinylpyrrolidone demonstrated superiority over starch USP and alginic acid in most of the experimental tablet formulations made by either dry or wet granulation. A quinazolinone compound was formulated into tablets employing each disintegrant to provide identical disintegration times, and these tablets were submitted to dissolution rate analysis. The dissolution results showed some differences for those made by direct compression but no variation for wet granulated tablets.

Keyphrases □ Polyvinylpyrrolidone, cross linked—evaluated as tablet disintegrant, compared to starch USP and alginic acid □ Tablet disintegrants—cross-linked polyvinylpyrrolidone evaluated, compared to starch USP and alginic acid □ Disintegration properties—cross-linked polyvinylpyrrolidone, compared to starch USP and alginic acid

Today's emphasis on the availability of drugs highlights the importance of the relatively rapid disintegration of a tablet as a criterion for ensuring uninhibited drug dissolution behavior (1–3). Only a few acceptable tablet disintegrating agents are available to the research pharmacist. The starches (corn, potato, wheat, rice, and arrowroot) have been extensively studied (4–7) as to their varying properties as disintegrants (8). The mechanism of action of the starches is still undergoing study, although at one point it was wrongly felt that grain swelling was responsible (7). Experiments with compressed starch, both dry and wetted, observed with

a scanning electron microscope resulted in this conclusion.

The purpose of the current research was to evaluate cross-linked polyvinylpyrrolidone as a disintegrant in comparison with starch (*i.e.*, corn starch) and alginic acid. Alginic acid possesses good disintegrating properties at reasonably low concentrations and provides other desirable physical characteristics to the tablet structure. Certain physical parameters of the disintegrants were evaluated to obtain an insight as to their potential disintegrating efficiency. Tablets prepared by dry and wet granulations using a poorly water-soluble drug contained sufficient quantities of each disintegrant to give identical disintegration times. The effects of the various disintegrating agents were then evaluated utilizing dissolution studies as a measure of *in vitro* availability.

EXPERIMENTAL

Materials—Three substances were studied for their comparative tablet disintegrating property: starch, alginic acid[1], and cross-linked polyvinylpyrrolidone[2]. Starch USP was used, and the alginic acid and cross-linked polyvinylpyrrolidone were accepted on the basis of manufacturer's specifications. The same lot of disintegrants and excipients were utilized for all experimental trials.

All other tablet excipients were USP or NF grade. The drug substances used in the preparation of the various tablet formulations were: 1-isopropyl-7-methyl-4-phenylquinazolin-2(1*H*)-one[3], butalbital, and 6-(6,10-dihydroxyundecyl)-β-resorcylic acid μ-lactone[4].

Selection of a Tablet Disintegration Agent—Starch and alginic acid have been well accepted as disintegrating agents and are used extensively in tablet formulations. Cross-linked polyvinylpyrrolidone was submitted to testing to justify its ranking with the other disintegrants available to the research pharmacist. The criteria by which the authors selected this new disintegrant stemmed from the ability of cross-linked polyvinylpyrrolidone to sorb a large quantity of moisture under isothermal, constant relative humidity conditions. Cross-linked polyvinylpyrrolidone is a white, free flowing, high molecular weight, cross-linked polymer of vinylpyrrolidone formed under the influence of a special catalytic environment. Cross-linked polyvinylpyrrolidone is highly insoluble in water, strong mineral acids, and alkali, so consequently there is a lack of information relating to its molecular weight. Its main commercial use, thus far, has been as a filtering aid for the wine and vinegar industries.

Determination of Maximum Moisture Sorption of Disintegrants—Ten grams of starch, alginic acid, or cross-linked polyvinylpyrrolidone was accurately weighed and evenly distributed over the surface of an 89-mm. tared petri dish. The sample was then placed in a large desiccator containing distilled water in its reservoir. The desiccator was then stored in a laboratory oven and the temperature was maintained constant at 37 ± 0.5°. At various time intervals, the weight gained by the exposed samples was recorded and the amount of water sorbed was calculated from the weight difference.

Determination of Hydration Capacity of Disintegrants—The procedure utilized (9) was developed for materials that do not contain appreciable (over 25%) water-soluble constituents. A 2-g. sample of disintegrant was placed into a 100-ml. centrifuge tube tared with stopper. Forty milliliters of water (pH 6–7) was added, and the tube was stoppered and shaken vigorously to suspend the sample thoroughly. The suspension was allowed to stand for 10 min. During this time, it was mixed by inverting three times at the end of 5 and 10 min. The stopper was then removed and the tube was centrifuged for 15 min. at 1000×*g*. The centrifuge was allowed to stop without braking. The supernate was carefully decanted and the tube was inverted to allow draining. The tube was then restoppered and the contents were weighed. The hydration capacity was calculated in the following manner:

$$\text{hydration capacity} = \frac{(\text{weight of tube} + \text{sediment}) - (\text{weight of tube})}{\text{sample weight (dry basis)}} \quad \text{(Eq. 1)}$$

Determination of Specific Surface Area of Disintegrants—In an attempt to establish the relationship that existed between the maximum moisture sorbed by the disintegrants and their specific surface area, the Brunauer, Emmett, and Teller (B.E.T.) technique[5] was performed.

The B.E.T. method involved low-temperature nitrogen adsorption by the powder sample. Samples were pretreated by evacuation at 0.001 mm. Hg under elevated temperature to outgas any adsorbed gases from the solid surface. The surface area analysis involved incremental gas volume adsorption measurements, which were made by accurately determining the equilibrium pressure following the introduction of gas quantities into the system.

Determination of Bulk Density of Disintegrants—The procedure utilized (10) is often referred to as the cylinder-drop technique. An accurately weighed sample of each disintegrant, of about 50-ml. volume, was introduced into a 100-ml. graduated cylinder. The cylinder was dropped onto a hard wood surface six times from a height of 2.54 cm. (1 in.) at 2-sec. intervals. The bulk density was then calculated by dividing the weight of the sample (grams) by the final tapped volume (milliliters) of the sample contained in the cylinder.

Direct Compression and Wet Granulation Tablet Formulation—Various tablet formulations exemplifying both direct compression and wet granulation techniques were selected to compare the disintegration property of the three disintegrants under investigation. The material compositions of these tablets are presented in Table I, with the categorizing of each tablet type into six series. Three drugs of varying water solubility were chosen for this segment of the experiments. In Series 1–6, wherever the concentration of disintegrant was varied, lactose powder was substituted to maintain the same total tablet weight.

Direct Compression Tablet Preparation for Disintegration Time Studies—The required amounts of drug, tablet diluent, and disintegrant were accurately weighed and passed through a No. 20-mesh U. S. Standard sieve. The materials were then transferred to a twin-shell blender[6] and tumbled for 10 min. The required amount of lubricant was accurately weighed, passed through a No. 60-mesh U. S. Standard sieve, and added to the blender. The materials were tumbled for an additional 5 min. The materials were then compressed into tablets of the appropriate weight and hardness, utilizing a single-punch tablet press[7] equipped with selected size tablet punches.

Wet Granulation Tablet Preparation for Disintegration Time Studies—The required amounts of drug, tablet diluent, disintegrant, and lubricant were accurately weighed and passed through a No. 20-mesh U. S. Standard sieve. The materials were then transferred to a twin-shell blender, equipped with an intensifier bar[6], and mixed for 5 min. The required amount of tablet binder (polyvinylpyrrolidone) was accurately weighed and dissolved in a suitable quantity of equal volumes of granulating solvents. This solution was added to the blender through the intensifier bar, and mixing was continued for 5 min. after the addition of the granulating solution. The wet granulation was placed on a paper-lined tray in an oven at 40° and dried to 1–3% moisture. The dry granulation was passed through a No. 18-mesh U. S. Standard sieve and compressed into tablets of the appropriate weight and hardness, utilizing a single-punch tablet press equipped with selected size tablet punches.

Tablet Preparation for Dissolution Rate Studies—Granulations were prepared utilizing both the direct compression and wet granulation techniques previously outlined. Tablets were prepared by compression in a hydraulic press[8] equipped with a gauge measuring forces from 0 to 909 kg. (0 to 2000 lb.) and calibrated in 22.7-kg. (50-lb.) increments. A special holder held the bottom punch and die in a fixed position during compression. The required amount of

[1] Kelacid, Kelco Corp., San Diego, Calif.
[2] Polyclar AT, GAF Corp., New York, N. Y.
[3] Chemical Development Dept., Sandoz-Wander, Inc., East Hanover, N. J.
[4] Commercial Solvents Corp., New York, N. Y.
[5] Model 400 surface-area analyzer, Micromeritics Instrument Corp., Norcross, Ga.
[6] Patterson-Kelley, Inc., East Stroudsburg, Pa.
[7] Model E, Stokes Equipment Corp., Warminster, Pa.
[8] Model C, Fred S. Carver, Inc., Summit, N. J.

Table I—Tablet Composition Used to Compare Disintegration Property for Cross-Linked Polyvinylpyrrolidone, Alginic Acid, and Starch

	Quantity per Tablet, mg.			
Series 1 (water-insoluble drug)	A	B	C	D
Resorcylic acid compound	100.0	100.0	100.0	100.0
Lactose powder	65.4	65.4	65.4	49.0
Cross-linked polyvinylpyrrolidone	3.6 (2%)	—	—	—
Starch	—	3.6 (2%)	—	20.0 (11%)
Alginic acid	—	—	3.6 (2%)	—
Polyvinylpyrrolidone	10.0	10.0	10.0	10.0
Magnesium stearate	1.0	1.0	1.0	1.0
Total tablet weight	180	180	180	180
Granulating solvents				
S.D. No. 30 alcohol				
Purified water				
Wet granulation tablets: 9-mm. deep concavity, 4–6 SCH[a]				
Series 2 (moderately water-soluble drug)	E	F	G	
Butalbital acid	50	50	50	
Lactose, spray dried	62	62	62	
Cross-linked polyvinylpyrrolidone	6 (5%)	—	—	
Starch	—	6 (5%)	—	
Alginic acid	—	—	6 (5%)	
Magnesium stearate	2	2	2	
Total tablet weight	120	120	120	
Direct compression tablet: 7-mm. standard concavity, 5–7 SCH				
Series 3 (placebo)	H	I	J	
Lactose, spray dried	200	200	200	
Calcium sulfate, dihydrate	83	83	83	
Cross-linked polyvinylpyrrolidone	15 (5%)	—	—	
Starch	—	15 (5%)	—	
Alginic acid	—	—	15 (5%)	
Stearic acid	1	1	1	
Magnesium stearate	1	1	1	
Total tablet weight	300	300	300	
Direct compression tablets: 8-mm. standard concavity, 11–13 SCH				
Series 4 (gastric fluid-soluble drug)	K	L	M	
Quinazolinone compound	75.0	75.0	75.0	
Lactose, spray dried	134.4	134.4	134.4	
Cross-linked polyvinylpyrrolidone	6.6 (3%)	—	—	
Alginic acid	—	6.6 (3%)	—	
Starch	—	—	6.6 (3%)	
Magnesium stearate	4.0	4.0	4.0	
Total tablet weight	220.0	220.0	220.0	
Direct compression tablets: 9-mm. flat-face, beveled-edge concavity, 9–11 SCH				
Series 5 (gastric fluid-soluble drug)	N	O	P	
Quinazolinone compound	25.0	25.0	25.0	
Lactose, spray dried	184.0	177.4	102.6	
Cross-linked polyvinylpyrrolidone	6.6 (3%)	—	—	
Alginic acid	—	13.2 (6%)	—	
Starch	—	—	88.0 (40%)	
Stearic acid	4.4	4.4	4.4	
Total tablet weight	220.0	220.0	220.0	
Direct compression tablets: 9-mm. flat-face, beveled-edge, 4–5 SCH				
Series 6 (gastric fluid-soluble drug)	Q	R	S	
Quinazolinone compound	25.0	25.0	25.0	
Lactose powder	185.5	182.2	120.6	
Cross-linked polyvinylpyrrolidone	1.1 (0.5%)	—	—	
Alginic acid	—	4.4 (2%)	—	
Starch	—	—	66.0 (30%)	
Polyvinylpyrrolidone	4.0	4.0	4.0	
Stearic acid	4.4	4.4	4.4	
Total tablet weight	220.0	220.0	220.0	
Granulating solvents				
S.D. No. 30 alcohol				
Purified water				
Wet granulation tablets: 9-mm. flat-face, beveled-edge concavity, 4–5 SCH				

[a] SCH, Strong–Cobb hardness, was determined with a Heberlein hydraulic drive tablet hardness tester.

Table II—Pertinent Physical Parameters[a] for Evaluating Relative Disintegrant Efficiency

Physical Property	Tablet Disintegrant—Cross-Linked Polyvinylpyrrolidone	Alginic Acid	Starch
Bulk density, g./ml.	0.26	0.68	0.63
Specific surface area, $m.^2/g.$	1.03	0.75	0.59
Maximum moisture sorption, % w/w	58.5	33.2	19.8
Hydration capacity	5.6	7.0	1.8

[a] Each determination is an average of four individual experiments.

material to make a tablet was weighed and transferred into the die cavity. The top punch was then gently inserted into the die cavity, and the granulation was compressed to a predetermined force.

The tablet thickness for each tablet was measured using a micrometer with vernier. Each tablet employed in the dissolution studies had to adhere to a tolerance of 0.02 mm. This physical measurement assured compliance of each tablet to a similar disintegration time for consecutive tablets.

The slow compression method was useful in controlling reproducibility of the physical character of each tablet. However, it provided substantially different stresses than those normally obtained with a high speed rotary tablet machine. Therefore, tablets prepared under production conditions may differ considerably from the test results.

Disintegration Test for Tablets Prepared to Evaluate Disintegrants—The USP XVIII (11) test procedure for uncoated tablets was utilized and modified to the extent that no disks were employed.

Friability Test for Tablets Prepared to Evaluate Disintegrants—The friability of all tablets studied was determined in a test apparatus consisting of a 27-cm. diameter, Plexiglas hollow chamber, 6 cm. in width. A curved arm in the chamber extends from a point on the circumference to slightly above the center of the apparatus. The apparatus is rotated at 25 r.p.m. by use of a shaft and motor at its center. The tablets were dropped a distance of 14 cm. from the arm at each rotation.

Twenty previously weighed tablets were placed in the apparatus, and the apparatus was then rotated for 4 min. to subject the tablets to 100 drops. The tablets were then weighed and the weight loss was calculated in terms of "percent friability."

Dissolution Rate Analysis of Tablets—The apparatus utilized is described in USP XVIII (13). A volume of 900 ml. of aqueous hydrochloric acid (pH 1.2, 37 ± 0.5°) was used as the dissolution medium, and a stirring speed of 50 r.p.m. was maintained.

Dissolution of the drug from the tablets was conducted through a 30-min. interval, where at least three half-lives were encompassed. Apparent sink conditions were adhered to in this study, as calculated by the solubility of the pure drug at 37° and pH 1.2.

The analytical details for following dissolution involved the withdrawal of 10-ml. aliquots at specified time intervals using a pipet with a filter tip. Then 10 ml. of aqueous pH 1.2 fluid was added to the beaker to replace the withdrawn volume. The aliquot was diluted to 20 ml. with aqueous pH 1.2 fluid. The absorption of the diluted solution was measured on a recording spectrophotometer[9] over the UV spectrum, and the maximum absorbance at 232 nm. was used to calculate the concentration of the quinazolinone compound. A correction factor was calculated for each sequential sampling as a result of the amount of dissolved drug removed for each sampling.

RESULTS AND DISCUSSION

Physical Parameters Employed for Evaluation of Disintegrants—Certain physical parameters were determined for the three materials studied in an attempt to predict their relative efficiency as tablet disintegrants (Table II). In comparing the various properties of cross-linked polyvinylpyrrolidone with the other two disintegrants, the most obvious large difference exists for the maximum moisture

[9] Cary model 14.

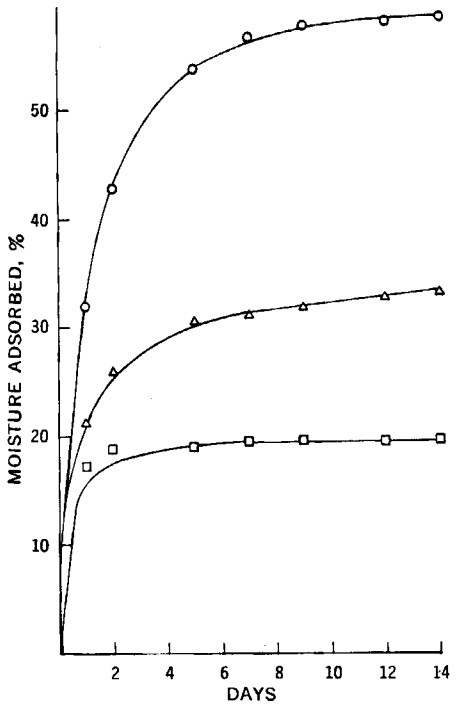

Figure 1—*Moisture sorption profile for the three disintegrants evaluated at 47 mm. aqueous tension and exposed to 37°. Key: ○, cross-linked polyvinylpyrrolidone; △, alginic acid; and □, starch.*

sorption. Figure 1 shows this parameter to be significantly greater for cross-linked polyvinylpyrrolidone than for either of the other compounds studied, resulting in the sorption of more than 50% of its own weight of water. This magnitude of difference between cross-linked polyvinylpyrrolidone and alginic acid is quite significant; however, the hydration capacity wherein water actually wets the material reveals about the same liquid–solid interactions or swelling power. Both parameters suggest that starch has substantially lower efficiency, in keeping with its poor action as a disintegrant in low concentrations. The lower bulk density of cross-linked polyvinylpyrrolidone acts as a positive factor for more adequate distribution within a tablet matrix.

The large specific surface area observed for cross-linked polyvinylpyrrolidone confirms the authors' theory that the greater capacity for water sorption under the conditions utilized in conducting the maximum moisture sorption experiments is a surface-related phenomenon. Figure 2 depicts the linear relationship existing between maximum moisture sorption and specific surface area for the three disintegrants. Under the normal environmental conditions to which the cross-linked polyvinylpyrrolidone and its tablets were exposed during storage, moisture sorption was determined to be negligible.

The four physical parameters discussed may possibly predict the relative usefulness and efficiency of new materials as disintegrants. The major emphasis apparently must be placed upon maximum moisture sorption and hydration capacity. Starch may be employed to establish a baseline for comparison of these properties with a new material.

Mechanism of Action Postulated for Disintegrants—Researchers have reported that starch's mechanism of action as a disintegrant involves only a limited amount of swelling of the grains (7) and that pores and porosity (12) of the tablet generally could not be correlated with disintegration times. Therefore, these phenomena are not the major mechanisms by which starch brings about tablet disintegration.

The authors believe that the mechanism of action of cross-linked polyvinylpyrrolidone depends greatly upon capillary effect in the presence of water. Maximum moisture sorption results obtained for cross-linked polyvinylpyrrolidone, alginic acid, and starch strongly suggest that the affinity of water for the disintegrant would permit distinction between their relative efficiencies. Hydration capacity would also support the thesis proposed inasmuch as it is related to swelling capacity. Cross-linked polyvinylpyrrolidone demonstrated

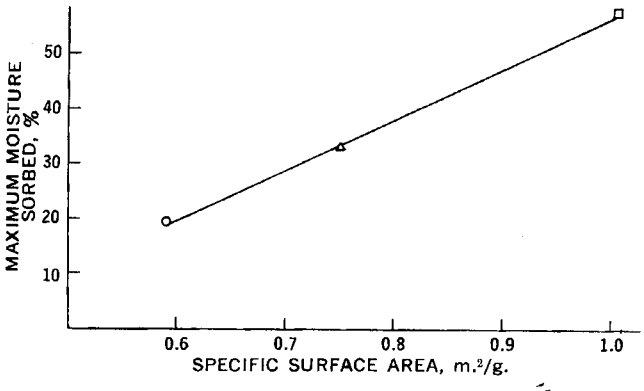

Figure 2—*Relationship of the maximum moisture sorption* versus *the specific surface area for the three disintegrants. Key:* □, *cross-linked polyvinylpyrrolidone;* △, *alginic acid; and* ○, *starch.*

similar behavior when compared with alginic acid. Since the data in Table III show cross-linked polyvinylpyrrolidone to be a superior disintegrant to alginic acid, swelling does not, in itself, appear to be the major mechanism of action.

The specific surface area results correlate well with the ranking of maximum moisture sorption for each disintegrant. The greater the surface area of the disintegrant, the more numerous are the sites for capillary attraction of water to its surface. The bulk density and maximum moisture sorption differences for cross-linked polyvinylpyrrolidone and alginic acid very possibly predict the differences that were observed for their relative disintegrant efficiency (discussed in the next section).

The mechanism of action of disintegrants is very complex and cannot be readily simplified into one or more categories. While it seems apparent that cross-linked polyvinylpyrrolidone acts through capillary activity with a secondary swelling effect, it is difficult to provide a conclusive statement as to the overall mechanism of action.

Relative Efficiency of Disintegrants in Various Tablet Formulations—The ultimate manner in which disintegrants can be properly evaluated is to prepare tablets for evaluation. Tablet formulations of various excipient composition and method of manufacture were employed to evaluate the relative efficiency of cross-linked polyvinylpyrrolidone, alginic acid, and starch as disintegrants. The tablet formulations manufactured for each series maintained the same physical parameters as shown in Table III for Series 1–4. The quantity of disintegrant was kept the same within each series for the purpose of material comparison. The disintegrant concentrations used were deliberately selected to illustrate the superiority of cross-linked polyvinylpyrrolidone. In all instances, this resulted in lower concentrations of starch than are normally employed.

Table III summarizes the disintegration time and friability as determined for all of the tablets studied. The outstanding difference between cross-linked polyvinylpyrrolidone and the other two disintegrants is its ability to bring about rapid disintegration with relatively low concentrations.

Cross-linked polyvinylpyrrolidone performed better than alginic acid and starch as a disintegrant in Series 1, 2, and 4. Each of these series contained drug, whereas in Series 3, which showed some similarity of disintegration times for cross-linked polyvinylpyrrolidone and alginic acid, no drug was incorporated.

Series 1 formulations represent a tablet containing about 55% drug which is almost totally water insoluble. These tablets were manufactured by a conventional wet granulation technique employing polyvinylpyrrolidone as the binder. Cross-linked polyvinylpyrrolidone was shown to surpass the alginic acid by threefold and the starch by 15-fold as a disintegrant. When 11% starch was employed, a reasonable disintegration time of 10 min. resulted; however, this resulted in a significant increase in tablet friability. The tablet formulation from Series 1, without the addition of a disintegrant, resulted in a lack of disintegration after 2 hr. of exposure. An important asset of cross-linked polyvinylpyrrolidone, which was pointed out during these studies, was that the wet granulation technique did not interfere with the desired tablet distintegration properties.

Series 2 shows cross-linked polyvinylpyrrolidone to be superior to alginic acid and starch from both a disintegration time and friability standpoint. Cross-linked polyvinylpyrrolidone disintegrated three times as fast as alginic acid, while with starch the tablet failed to disintegrate after 2 hr. of exposure. Cross-linked polyvinylpyrrolidone has been proven to be directly compressible in pure form, and this phenomenon relates to the low percent friability exhibited with its tablet formulations. In fact, cross-linked polyvinylpyrrolidone is presently being evaluated in higher concentrations in tablets as a direct compression binder–diluent–disintegrant.

Table III—Disintegration Time and Friability for Various Tablet Formulations Containing Cross-Linked Polyvinylpyrrolidone, Alginic Acid, and Starch

	Disintegration Time, min.[a]	Friability, %
Series 1 (water-insoluble drug)		
Formula A (2% cross-linked polyvinylpyrrolidone)	4	0.17
Formula B (2% starch)	60	0.20
Formula C (2% alginic acid)	12	0.17
Formula D (11% starch)	10	0.54
Series 2 (moderately water-soluble drug)		
Formula E (5% cross-linked polyvinylpyrrolidone)	3	0.20
Formula F (5% starch)	>120	0.37
Formula G (5% alginic acid)	9	0.30
Series 3 (placebo)		
Formula H (5% cross-linked polyvinylpyrrolidone)	0.67	0.20
Formula I (5% starch)	10	0.34
Formula J (5% alginic acid)	0.67	0.16
Series 4 (gastic fluid-soluble drug)		
Formula K (3% cross-linked polyvinylpyrrolidone)	1	0.46
Formula M (3% starch)	120	2.10
Formula L (3% alginic acid)	3	0.80

[a] Represents average of six individual tablets.

Series 3 represents a placebo tablet formulation using 5% disintegrant because starch was not operative below this level. The lower friability values for cross-linked polyvinylpyrrolidone and alginic acid indicate the presence of a tablet-binding property, whereas the starch renders a tablet considerably more friable. When the starch content was increased to 10% to reduce the disintegration time, an unacceptable friability was obtained which is typical for this material.

Series 4 demonstrated that a 3% level of cross-linked polyvinylpyrrolidone surpassed both alginic acid and starch in disintegration time. Furthermore, the friability was extremly poor for alginic acid and starch, whereas cross-linked polyvinylpyrrolidone bordered on an acceptable range. Of course, Series 4 tablets contained no auxiliary binder; by increasing the concentration of cross-linked polyvinylpyrrolidone to 5%, the friability was reduced by 65%. The same change with the other two disintegrants did not reduce the friability satisfactorily.

The authors have employed cross-linked polyvinylpyrrolidone and alginic acid as tablet disintegrating agents in an unconventional tablet matrix, and the information will be published at a later date. However, it should be noted that 20% cross-linked polyvinylpyrrolidone was necessary to obtain a 4-min. disintegration; when alginic acid was substituted at the same concentration, it required 60 min. to accomplish disintegration. When the alginic acid content was increased to 30%, no reduction of disintegration time was demonstrated.

The interesting properties of cross-linked polyvinylpyrrolidone stem from its ability at low concentrations (2–5%) to bring about acceptable tablet disintegration as well as its inherent ability to function as a tablet binder. The tablets resulting from its use possess low percent friability characteristics.

Effect of Disintegrants on Dissolution Behavior of Tablets—To ascertain the overall acceptability of a new disintegrant, it must be shown that no interference with the dissolution behavior of the drug from the tablet is involved. To investigate this parameter for cross-linked polyvinylpyrrolidone, tablets were formulated using the

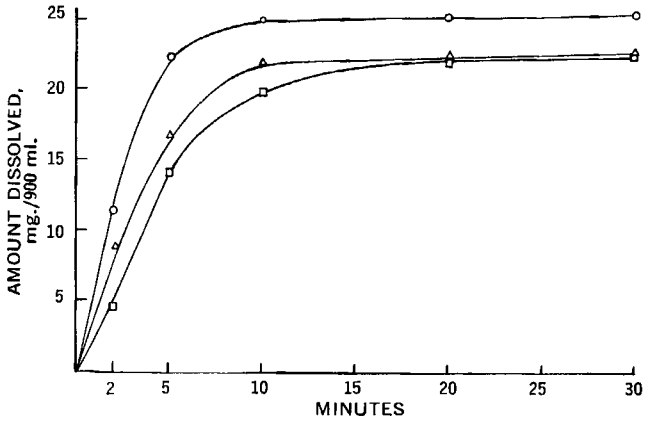

Figure 3—*Dissolution of quinazolinone compound in 900 ml. aqueous solution at pH 1.2 from directly compressed tablets of identical disintegration time. Key: ○, 3% cross-linked polyvinylpyrrolidone; △, 6% alginic acid; and □, 40% starch. Each data point plotted is the average of four experimental runs.*

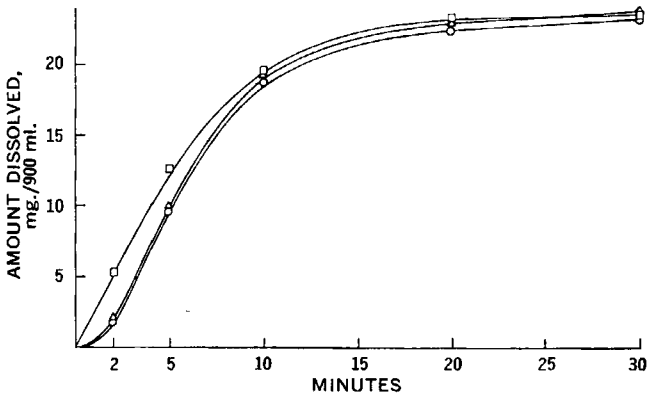

Figure 4—*Dissolution of quinazolinone compound in 900 ml. aqueous solution at pH 1.2 from wet granulated compressed tablets of identical disintegration time. Key: △, 0.5% cross-linked polyvinylpyrrolidone; ○, 2% alginic acid; and □, 30% starch. Each data point plotted is the average of four experimental runs.*

direct compression and wet granulation methods. In this instance, cross-linked polyvinylpyrrolidone was again compared to alginic acid and starch. This required the formulation of tablets providing identical disintegration times so that the only parameter dissimilar would be the concentration of disintegrant.

Series 5 represents the formulation manufactured by direct compaction. To obtain meaningful dissolution rate data, uninhibited by disintegration, all of these tablets were formulated to give a 1-min. disintegration; 3% cross-linked polyvinylpyrrolidone, 6% alginic acid, and 40% starch were required. Friability of these tablets was not performed since the starch formulation would have been unsatisfactory. Figure 3 depicts the dissolution rate profile obtained with the Series 5 tablets. The cross-linked polyvinylpyrrolidone definitely enhanced the dissolution rate for the isoquinazolinone tablets; this parameter can be readily compared by studying Table IV where $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ values for each disintegrant studied are tabulated. The data suggest that the dissolution behavior is not solely dependent upon the tablet's disintegration time but involves a more complex phenomenon. Perhaps a surface interaction of the disintegrant with the dissolved or undissolved drug resulted in influence upon its dissolution behavior. The data indicate incomplete dissolution with the alginic acid and starch tablets for the time period studied.

Figure 4 depicts the dissolution behavior for the tablets manufactured from Series 6 by a wet granulation method. The tablets contained 25 mg. of the isoquinazolinone compound and were formulated to disintegrate within 2 min. They required the following quantities of disintegrant: 0.5% cross-linked polyvinylpyrrolidone, 2% alginic acid, and 30% starch. Polyvinylpyrrolidone was employed as the binder for Series 6 tablets. The dissolution rate profiles for the three disintegrants in this case did not differ significantly. The important factor that can be emphasized here results from the low quantity (0.5%) of cross-linked polyvinylpyrrolidone that accomplished this acceptable disintegration time and dissolution behavior, even though the tablets were prepared by a wet process.

The results obtained demonstrate that tablets with the same disintegration times do not necessarily imply the attainment of similar drug dissolution rate profiles. In the case of Series 5, identical disintegration times yielded different dissolution rates, while this did not occur for Series 6. In any event, both series demonstrated the superiority of cross-linked polyvinylpyrrolidone due to the lower concentrations needed for rapid disintegration. At no point was there an indication of any interaction between drug and cross-linked polyvinylpyrrolidone that would result in an inhibition of availability.

Table IV—Dissolution Rates[a] of a Quinazolinone Compound in 900 ml. Aqueous Solution at pH 1.2 for Tablets Containing Cross-Linked Polyvinylpyrrolidone, Alginic Acid, and Starch Prepared by Direct Compression

Disintegrant	$t_{50\%}$, min.	$t_{75\%}$, min.	$t_{90\%}$, min.
Cross-linked polyvinylpyrrolidone	2.2	3.8	5
Alginic acid	3.4	6.8	11.3
Starch	4.5	8.5	17.5

[a] Each time interval was obtained from Fig. 3.

SUMMARY

Cross-linked polyvinylpyrrolidone was found to possess very acceptable properties for use as a tablet disintegrant. It appears that the parameters of maximum moisture sorption and hydration capacity collectively can be employed as a guideline for the selection of new materials as potential tablet disintegrants. A concentration of from 0.5 to 5% cross-linked polyvinylpyrrolidone was adequate as a disintegrant for the tablet formulations screened in this research. The apparent binding property exhibited by cross-linked polyvinylpyrrolidone resulted in low percent tablet friability when it was employed as a disintegrant even in low concentrations. The lack of effect on drug dissolution behavior by cross-linked polyvinylpyrrolidone verified that it did not interfere with the dissolution of a quinazolinone compound utilized in both the dry and wet granulated tablets studied.

Cross-linked polyvinylpyrrolidone may very well find its ultimate use in tablet formulations as a binder–disintegrant. Cross-linked polyvinylpyrrolidone surpasses, in this usage, microcrystalline cellulose since larger quantities of microcrystalline cellulose are usually required in combination with spray-dried lactose. Series 3, with 5% cross-linked polyvinylpyrrolidone in a placebo tablet, demonstrated the excellent properties of both rapid disintegration and low percent tablet friability. Cross-linked polyvinylpyrrolidone in most of the tablets studied excelled in performance over alginic acid. The inert nature of cross-linked polyvinylpyrrolidone justifies its use as a tablet disintegrant of choice when an acid, such as alginic acid, would interfere with the chemical stability of the drug.

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▲ To whom inquiries should be directed.

Effect of Selected Amino Acids on Ethanol Toxicity in Rats

RUDOLPH J. BREGLIA*, CHARLES O. WARD*▲, and CHARLES I. JAROWSKI†

Abstract □ The effects of L-lysine, L-arginine, L-ornithine, and glycine on acute ethanol intoxication, and the degree of ethanol-induced CNS depression, were investigated. Amino acid treatment was shown to prolong the onset of ataxia, reduce the duration of sleeping time, and decrease the number of rats losing the righting reflex, but it did not alter the LD_{50} values in response to ethanol. The protective actions of the amino acids are attributed to the formation of an amino acid–acetaldehyde complex, although other possible interactions are discussed.

Keyphrases □ Ethanol toxicity—effect of amino acids, rats □ Amino acids—effect on ethanol toxicity, rats □ CNS depression, ethanol induced—effect of amino acids, rats □ Toxicity, ethanol—effect of amino acids, rats

The effect of amino acids on the concentration and rate of disappearance of ethanol from the blood was the subject of the investigations of Schiller *et al.* (1, 2). After simultaneous administration of 120 ml. p.o. of ethanol (50% v/v) together with an amino acid–dextrose mixture (protein hydrolysates[1]), given intravenously to chronic alcoholics without hepatic dysfunction or nutritional deficiency, ethanol utilization curves showed that the amino acid mixture significantly decreased the maximum blood ethanol levels obtained and accelerated the rate of disappearance of ethanol from the blood. The activity of the amino acid–dextrose mixture was confirmed in an *in vitro* preparation of rat liver slices incubated with ethanol; while the specific amino acids responsible for these effects could not be identified, these experiments indicated that they contain four carbons or less.

Alanine has been shown to follow the pattern reported for pyruvate in increasing the disappearance of ethanol from the blood (3, 4). This is presumed to be the result of transformation of alanine to pyruvate, a Kreb's cycle intermediate which is thought to accelerate the disappearance of ethanol by increasing its aerobic metabolism (5).

When glycine or alanine was administered orally simultaneously with 15 g. of ethanol to dogs, the maximum concentration of ethanol appearing in the blood was lower than the control group (6, 7). The author concluded that the disappearance of ethanol must take place during absorption (6) and that a stable compound of ethanol and the amino acids may be formed to account for the decrease in the concentration of ethanol in the blood (7).

The nature of dietary protein fed to rats which were given a constant volume (4.0–6.6 g./kg.) of 40% ethanol four times weekly for 16 months was found to be related to the ability to reduce the degree of inebriation and the numbers of deaths due to ethanol toxicity (8). In this study, egg protein was the most effective while a mixture of peanut meal and soy protein was the least effective in reducing the toxic and CNS depressant effects of ethanol. It was concluded that the protective effects of the dietary proteins were not related to an effect on the rate of ethanol absorption or the emptying time of the stomach but were due to differences in ethanol utilization once it was absorbed.

Jarowski and Ward (9) reported that 30 min. of pretreatment with L-tryptophan (165 mg. i.p.) before a 2-g./kg. i.p. dose of 95% ethanol in unfasted rats produced a significant potentiation of the acute depressant effects of ethanol as measured by changes in the LD_{50}, sleeping, and immobility times. The fasting essential amino acid profile of blood plasma, which has been useful in predicting the relative dietary value of proteins (10), was determined in that study and served as a basis for the use of L-tryptophan supplementation (9). In the fasting essential amino acid profile of blood plasma, the concentrations of amino acids in the plasma

[1] Aminosol, Abbott Laboratories, Inc., North Chicago, Ill.