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Keyphrases

β-Aminoketones—synthesis
Antibacterial activity—β-aminoketones
IR spectrophotometry—structure

Influence of Starch Concentration on the Disintegration Time of Tolbutamide Tablets

By K. C. COMMONS, A. BERGEN, and G. C. WALKER

Disintegration tests were performed on tablets compressed from 16/20, 40/60, and 60/80 mesh granulations prepared by the method of dry granulation to contain 250 mg. of tolbutamide and corn starch concentrations of 6, 7, 8, 9, and 10 percent in each granulation size. It might be expected that disintegration time would decrease as the percentage of starch in the tablet increased. This does not appear to be the case for tolbutamide tablets. Instead, there appears to be a critical starch concentration for different granulation sizes.

In a number of instances, poor tablet formulation has been shown to cause a significant variation in gastrointestinal absorption and physiological availability of the active ingredient (1–3). Variables in the formulation and processing include such factors as particle size and shape, binders, diluents, disintegrating agents, lubricants, compression rate, and compression pressure as well as physical features of the dosage form itself. Alteration of any of these factors may influence the disintegration time, dissolution rate, and clinical effectiveness of compressed tablets.

Disintegrating agents have been widely used in compressed tablets as substances or mixtures of substances added to a tablet to facilitate its breakup or disintegration following administration (4). There have been many classifications of disintegrating agents but one of the more recent is that of Feinstein and Bartilucci (5) who divided them into starches, clays, celluloses, algins, or gums. Fakouhi *et al.* (6) point out that disintegrating agents generally fall into three classes: (*a*) agents that react with moisture to constitute a foam, (*b*) effervescent substances that react with moisture to form a gas, and (*c*) substances that react with moisture to swell (most common). The most commonly used agent has been starch from various sources but particularly corn or potato starch.

A study was undertaken to determine the influence of corn starch concentration on the disintegration of tolbutamide tablets prepared from various size granules by direct compression.

EXPERIMENTAL

Tolbutamide powder (USP XVI, 100 mesh) was dried at 100° for 24 hr. Approximately 1 Gm. of powder at a time was compressed at 10,000 lb. gauge pressure in a Carver hydraulic press using 3/4-in. flat-face punches. The slugs were granulated using a Fitzpatrick mill and the granules sieved for 5 min. through 16, 20, 40, 60, and 80-mesh screens using an automatic sieve shaker. Granule sizes were designated 16/20, 40/60, and 60/80 which refers to a passage through the first sieve size number designation and retention on the second sieve. The tolbutamide granules and corn starch (USP XVI, moisture content 9.2% w/w) were thoroughly mixed to give granulation-starch mixtures containing 6, 7, 8, 9, and 10% corn starch. Compressed tablets of 250-mg. tolbutamide content were prepared from the various granule-starch combinations using 3/8-in. shallow concave punches at 2,000 lb. gauge pressure in the Carver press. Tablets and granules were assayed, and disintegration tests performed, using the methods as outlined in the USP XVII (7).

RESULTS AND DISCUSSION

Table I shows the average disintegration time of compressed tablets prepared from different granule sizes and containing varying percentages of corn starch. This information is presented graphically in Fig. 1.

It might be expected that disintegration time would decrease as the percentage of starch in the tablet is increased. This does not appear to be the case for tolbutamide tablets. Instead, there appears to be a critical starch concentration for different granulation sizes when granulations are prepared by methods involving dry granulation and com-

Table I—Average Disintegration Times in Minutes of Tolbutamide Tablets

Starch Concn., %	Granule Size 16/20	20/40	40/60	60/80
6	>30	>30	—	—
7	2.3	22.3	>30	>30
8	1.1	8.8	28.8	>30
9	0.4	0.3	1.9	2.1
10	—	—	0.7	1.0

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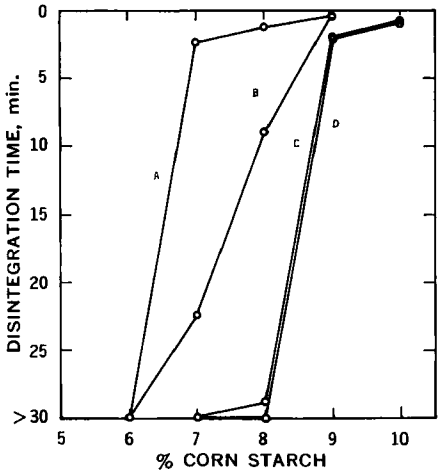

Fig. 1—Disintegration times, determined by the USP XVI method, of tolbutamide tablets prepared from different granule sizes and containing varying corn starch concentrations. Key: A, 16/20 granules; B, 20/40 granules; C, 40/60 granules; D, 60/80 granules.

pression. In most cases, tablets failed to disintegrate at a particular percentage of starch but disintegrated when the starch concentration was increased by about 1%. For example, tablets prepared from 16/20-mesh granules containing 6% corn starch failed to disintegrate within 30 min., whereas tablets containing 7% corn starch disintegrated in an average time of 2.3 min.

Curlin has suggested that the disintegration of tablets containing starch is due to capillary action (8). The more widely held view is that disintegration is caused by absorption of water by the disintegrating agent and development of pressure within the tablet caused by swelling or expansion of the disintegrating agent (8–10). Fakouhi *et al.* (6) in their studies of lactose tablet disintegration with powdered corn cob, powdered redwood bark, wood flour, powdered Douglas fir, methylcellulose, and corn starch point out that a decrease in disintegration time would be expected with an increase in concentration of the agent, but in the case of methylcellulose, redwood bark, and Douglas fir this was not experienced. The authors suggest that these substances possess adhesive or binding properties with a tendency to form adhesive gels when hydrated thus suggesting an optimum or maximum quantity of these substances beyond which tablet disintegration will be retarded. The mechanism of disintegration action for all agents is probably the same, *i.e.*, swelling in contact with water and subsequent rupture but with the necessary absorption of sufficient moisture. Forlano and Chavkin (11) used separate granulations of sodium bicarbonate, lactose, and magnesium trisilicate in mesh sizes ranging from 6–8 to 140–200 in increments of 2 mesh sizes with one at 200 mesh and finer to study the influence of granule size and capping in compressed tablets. In the case of sodium bicarbonate and lactose tablets, granules of 16–60 mesh showed the longest disintegration times. As the granule size decreased below 60 mesh the disintegration time decreased with an unexpected rise at 100–140 mesh, followed by a decrease at 140–200 mesh. In the case of magnesium trisilicate, tablets made using 12–30-mesh granules had longer disintegration times than the smaller mesh sizes. However, tablets made from granules smaller than 30 mesh showed decreased disintegration times. It is possible that the nature of the bonding is different between tablets and that the binders have different actions. In the case of magnesium trisilicate tablets the small hard core together with the nature of the substance probably prevented penetration of the center by water.

When starch is incorporated into a tablet, it is found in the channels between the granules. Starch is a relatively incompressible substance and tends to increase the porosity of the tablet. If there were no starch present in the channels, the tolbutamide granules would be deformed under compression to partially block the channels. Tablets were prepared from corn starch soaked in a saturated aqueous iodine solution and dried. Fracture of the tablet followed by macroscopic and microscopic examination suggested that the starch grains form continuous chains along the channels between the granules even at concentrations below those required to make the tablet disintegrate. However, it appears that as the percentage of starch is increased, thicker chains of starch are formed in the pore channels, thus enlarging the pores. This pore enlargement could allow water to enter the tablet more readily. Patel and Hopponen (12) have shown that where contact of starch grains in the interparticle spaces is continuous, disintegration is most rapid. They have also found that dried corn starch increased in volume by 78% when suspended in water. This increase in volume strongly suggests that swelling is the principal mechanism of action of corn starch as a disintegrator. Wurster and Seitz (13) have demonstrated that a small pore size which could be occluded by air would hinder entry of water into the tablet. This would be particularly true in the case of a hydrophobic substance such as tolbutamide. In this case, disintegration of the tablet would be slowed but could continue as the pores are enlarged by expanding starch grains near the surface of the tablet. Wurster and Seitz concluded that capillarity itself does not appear to have a disintegrating effect although it may be a factor in aiding entry of water into the tablet when pore size is favorable.

The critical starch concentration may have practical significance in both wet and dry granulation procedures, but particularly in view of the increasing tendency to use methods of dry granulation and direct compression in the pharmaceutical industry. Similar results have been secured using acetylsalicylic acid, salicylamide, and phenylbutazone. Preliminary *in vivo* studies using acetylsalicylic acid have shown good correlation between disintegration, dissolution, urinary excretion, and critical starch concentration. These results will be published shortly.

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Keyphrases

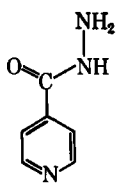
Tolbutamide tablets—disintegration
Corn starch grains—channel formation
Disintegration time—starch concentration

Influence of Metallic Ions on the Antituberculous Activity of Isonicotinoyl Hydrazones

By V. A. E. VOYATZAKIS*, G. S. VASILIKIOTIS†, G. KARAGEORGIOU‡, and IR. KASSAPOGLOU‡

Eleven isonicotinoyl hydrazones were prepared and they were tested *in vitro* as antitubercular agents. The effects of cupric and cobalt ions on their activity were investigated.

THE SPECIFIC activity of isonicotinic acid hydrazide (isoniazid I) against tubercle bacilli suggests interference with an essential metabolite. It has been shown (1, 2) that isoniazid combines with cupric ions to give 1:1 Cu-isoniazid complex (II) and 1:2, respectively. It also has been claimed that the action of isoniazid against *M. tuberculosis in vitro* is increased when copper is supplied in excess of that normally present in the medium (2).



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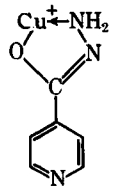


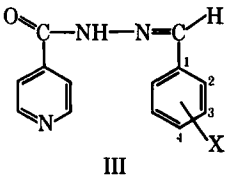
II

Moreover it has been shown (3) that 8-hydroxyquinoline (oxine) and related substances are toxic to bacteria only when traces of iron or copper ions are present in the medium. In this case the 1:1 metal complex has been shown to be the true toxic agent (4). The hypothesis was put forward that oxine is active due to the combination with these metal ions in the medium and that the complexes thus formed catalyze the oxidation of essential cell constituents. Cobalt can prevent injury to the cells, and it was suggested that this ion may be an essential cell constituent whose function is to protect, from oxidative destruction a vitally important chemical group. However, Albert (5) pointed out that while chelation might play some part in the activity of isoniazid, there must be some more important factor since the closely related picolinic acid hydrazide was less effective against tubercle bacilli but showed a metal affinity 10^3 to 10^6 times that of isoniazid.

Youatt (6) who investigated the effect of cupric ions on the uptake of hydrazides, found that copper prevented the development of strains resistant to isoniazid and increased the sensitivity to hydrazides of a strain which was already resistant to isoniazid. Stimulation of isoniazid uptake was still observed if the cells were exposed to copper ions and then washed before the addition of the isoniazid. This suggests that copper may first be bound to the cell and that chelation may occur on or in the cell.

Among the most active derivatives of isoniazid are its hydrazones. Fox and Gibas (7) have shown that 1-isonicotinoyl-2-isopropylidene hydrazone was very active against tubercle bacilli. Shchukina *et al.* (8) synthesized a number of isonicotinoyl hydrazones from aldehydes and ketones. Their biological tests, as antitubercular agents indicated that some of these are more active *in vivo* and far less toxic in mice. Sah and Peoples (9) reported also that a large number of isonicotinoyl hydrazones possess very high *in vivo* activity against *M. tuberculosis*, H 37 Rv, higher than that of streptomycin, and at least of the same order of magnitude as isoniazid. Recently Chakravarty, Bose, and Bose (10) synthesized some isonicotinoyl hydrazones which showed antituberculous activity comparable to that of isoniazid (Table I).

In this paper there is reported: (*a*) the synthesis of 11 isonicotinoyl hydrazones derived from substituted aromatic aldehydes and ketones having the general formula (III); (*b*) their microbiological examination *in vitro* as antitubercular agents, and (*c*) the influence of cupric and cobalt ions on their activity.



III

EXPERIMENTAL

Preparation of Isonicotinoyl Hydrazones—The hydrazones used in this study were synthesized according to the method of Sah and Peoples (9). All of them were recrystallized twice from methanol

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