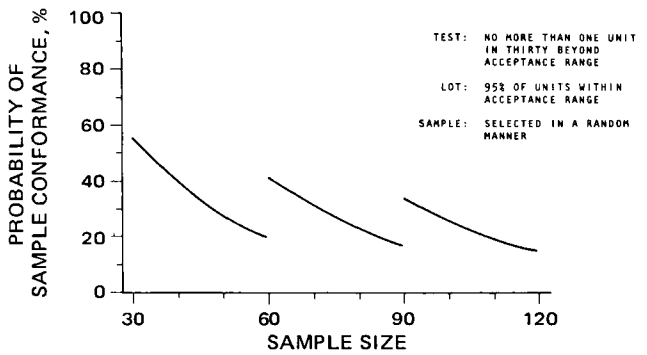

Figure 1—*Example of the effect of sample size on the content uniformity test.*

and:

> *"Where it is directed in an assay or a test that a counted number of dosage units is to be examined, the specified number is a minimal figure chosen only for convenience of analytical manipulation; it is not intended to restrict the total number of units that may be subjected to the assay or test. Regardless of the number of units so examined, the article meets the requirements if the same proportion of units conforms as is stated in the assay or single-stage test, or at the conclusion of a multiple-stage test."*

The employment of sample sizes greater than those stipulated in the monograph increases the discriminatory ability of the acceptance tests and provides a "cushion" in the event that some unit assays are not completed. However, the probability of drawing an unsatisfactory sample is a function of sample size. For example, consider the application of the compendial test for content uniformity to a randomly mixed lot with 5% of the units beyond the acceptance range.

The probability of sample conformance is 0.55, 0.42, 0.34, and 0.28 for samples of 30, 60, 90, and 120 units, respectively (Fig. 1). The lower probability of conformance of a sample of, for example, 59 units as compared to one of 60 units is due to the discrete nature of the dosage units. Only one nonconforming unit in a sample of 59 is acceptable, whereas two are acceptable in a sample of 60. Different, but similar, saw-toothed curves would be obtained for other percentages of units beyond the acceptance range. (For values less than 3.33%, the probability of sample conformance approaches 100% for increasing sample size, whereas the probability approaches 0% for values greater than 3.33%.) A similar situation exists for the other three tests.

(1) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975, p. 4.

(2) "The National Formulary," 14th ed., Mack Publishing Co., Easton, Pa., 1975, p. 11.

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Starch Paste Granulations: Binder Dilution Effects on Granulations and Tablets

Keyphrases □ Starch paste granulations—effect of gelatin binder solution concentrations, tableting characteristics □ Granulations, starch paste—effect of gelatin binder solution concentrations, tableting characteristics □ Dosage forms—tablets, effect of gelatin binder solution concentrations on starch paste granulations and tableting characteristics

To the Editor:

It was reported previously that the dilution factor of a gelatin binder solution used in a fluidized-bed granulating process influenced the friability of the granules (1). Specifically, the more dilute binder solutions resulted in less friable granules. The present communication reports similar results with aqueous dilutions of starch paste and a conventional granulating process.

Starch paste has long been used as a tablet binder in the pharmaceutical industry, but the literature contains few references to studies of this use. Starch paste granulations usually result in faster disintegrating tablets than do many other binders (especially the gum type) and may be preferred for this reason. Despite its wide usage, the effect of starch paste preparation variables on granulation or tablet quality has received little attention. One variable is the viscosity or thickness of the paste. In some cases, starch paste may be made with the maximum amount of water that can be used without overwetting the granulation. In other cases, less water is used and additional water is added to the granulation after some massing, based on the operator's judgment.

The formulations shown in Table I were manufactured in a small planetary-type mixer to find whether dilution of the starch paste affects granulation or tableting characteristics.

The lactose and starch were dry mixed in the mixer bowl for 5 min. The amount of water used to make the paste was varied from a 4:1 to a 6:1 water to starch ratio. The total amount of water used in each experiment was kept constant by varying the amount of water added to the mass after the starch paste had been mixed with the lactose–starch mixture for 1 min. The starch paste was cooked to a temperature of 72 ± 1°, and the total massing time was kept at 5 min

Table I—Starch Paste Dilutions

	Experiment A	Experiment B	Experiment C
Lactose, g	860	860	860
Starch (in dry mix), g	47	47	47
Starch (in paste), g	26	26	26
Water (for paste), ml	100	130	160
Water (used to *qs*), ml	100	70	40

Table II—Percent Fines Formed by Attrition

Experiment	500 Revolutions	1000 Revolutions
A	8.4	11.0
B	5.6	7.1
C	3.4	4.5

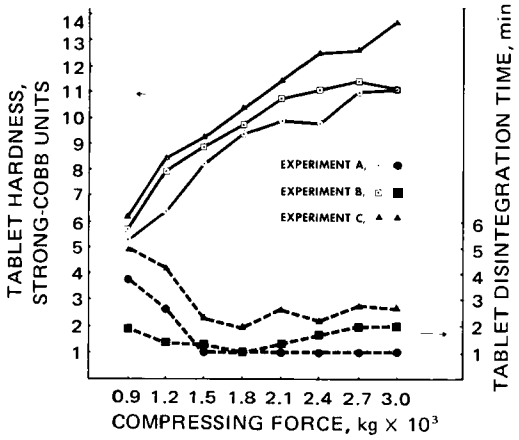

Figure 1—*Tablet hardness–pressure profile and corresponding disintegration times. Key: ⊙—⊙, tablet hardness; and ● - - ●, disintegration time.*

in each experiment to eliminate these variables. The wet mass was put through a 6-mesh screen, dried at 50° to a moisture content of 1%, and then passed through a 16-mesh screen.

Granulation friability was chosen as a measure of granulation quality. Friability was measured by tumbling 25 g of granulation larger than 150 mesh end over end in a Plexiglas cylinder, 3.81 cm in diameter and 30.48 cm long. The powder finer than 150 mesh generated by the tumbling was sifted off and weighed after 500 and 1000 revolutions and is shown in Table II as the percent of fines formed. The thinnest starch paste (C) yielded the strongest granulation and the thickest paste (A) yielded the most friable granulation, even though the same total amount of water was used in all three experiments. A sieve analysis showed that the percentage of particles coarser than 20 mesh also increased as the starch paste was made more dilute (Table III). This finding agrees with that of Marks and Sciarra (2) who concluded that the degree of granule friability decreased as the size of the granule increased.

Table III—Sieve Analyses

Experiment	Percent Remaining on 20 Mesh	40 Mesh	60 Mesh	100 Mesh	150 Mesh	Pan
A	21.3	40.6	17.3	9.6	10.7	0.5
B	28.9	41.6	13.2	7.1	6.6	2.5
C	30.7	40.7	12.1	7.0	5.5	4.0

The three granulations were lubricated with talc and magnesium stearate and compressed on an instrumented rotary tablet machine[1] at eight different compressing forces to obtain a pressure–hardness profile. This experiment showed that granulation compressibility improved with increasing starch paste dilution (Fig. 1). Tablet disintegration time was determined in the USP tablet disintegration apparatus using 37° water without disks (Fig. 1). The average disintegration time of six tablets was used. Disintegration time increased slightly with each dilution of the starch paste.

These data illuminate the influence of a seemingly inconsequential detail, the dilution factor of starch paste binder. Changes in starch paste thickness ordinarily may not have an adverse effect on tablet production, except for certain products that have rigid hardness or disintegration time specifications.

(1) W. L. Davies and W. T. Gloor, Jr., *J. Pharm. Sci.*, **62**, 170(1973).

(2) A. M. Marks and J. J. Sciarra, *ibid.*, **57**, 497(1968).

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[1] Stokes model B-2.