Effects of Concentration, Aging, and Temperature on Tablet Disintegrants in a Soluble Direct-Compression System

By L. A. BERGMAN and F. J. BANDELIN

ANY INVESTIGATION designed to study tablet disintegrants from the standpoint of a comparative evaluation must, of necessity, consider first all the factors that have any effect on disintegration. These variables include the nature of the active ingredient, disintegrant, binder, lubricant, tablet dimensions, hardness, manufacturing procedure, method of incorporating the disintegrant, speed of compression, age of the finished tablets, etc. (1–8).

While each of these factors individually, by contributing some effect characteristic of their particular nature, can affect disintegration, it is generally accepted that it is the combined effects exerted by these factors, opposed to singling out one in particular, which are responsible for influencing rate of disintegration (1–3).

To gain some insight into the complexities of tablet disintegration, a knowledge of the effects exerted by these individual factors is essential. Once this is understood, these variables can be considered then as a composite, and the effects which they exert with respect to one another will become more obvious.

Active ingredients as well as binders contribute at least one effect due to their solubility rates (1, 2). With certain exceptions, tablets of a soluble nature tend to dissolve rather than disintegrate, and the phenomenon of disintegration is a more rapid action than that of dissolution.

The effect of lubricants on disintegration may be attributed to their water-repellant nature (1) as well as the fact that they are added just prior to compression to coat the granulation physically.

It has been demonstrated by Higuchi *et al.* (1) that the majority of the granules compressed into a tablet retain their individual integrity. Therefore, it may be assumed that the disintegration of tablets takes place in two steps: first, the tablet breaks down to the granules; then the granules break down to smaller particles. If this is so, it will be appreciated readily how important the method of incorporating the disintegrant would be to obtain optimum disintegration. In general, it has been found that when part of the disintegrant is added prior to wet granulation and the balance added to the dried sized granules, optimum disintegration results (5, 6).

Since all of the work reviewed was performed on tablets prepared by wet granulation, it, therefore, seemed important to investigate how some of these factors would be affected in a soluble directly compressed system since this area has not been investigated previously.

Received September 29, 1964, from the Research Laboratories, Plough, Inc., Memphis, Tenn.
Accepted for publication October 24, 1964.

EXPERIMENTAL

In this study, a comparative evaluation was made of seven disintegrants (Table I) compressed at three concentrations (5, 10, and 15%) in a base of spray-dried lactose using magnesium stearate as the lubricant. The spray-dried lactose and magnesium stearate remained constant in each formula; the concentration of disintegrant was based on per cent of excipient (Table II).

TABLE I.—TABLET DISINTEGRANTS

Tablet	Mfr.
Avicel	American Viscose
Solka Floc BW-100	Brown Co.
Solka Floc BW-200	Brown Co.
Natrasol 250H	Hercules Powder Co.
CMC 7HDZP	Hercules Powder Co.
Corn starch U.S.P.	...
Calcium Sulfate Granulation S-294-1	Miles Laboratories

TABLE II.—BASIC FORMULAS

	mg./Tablet
Spray-Dried Lactose	325.0
Disintegrant (5% of lactose)	16.25
Magnesium stearate (1% of lactose)	3.25
Tablet wt., 344.5 mg.	
Spray-Dried Lactose	325.0
Disintegrant (10% of lactose)	32.5
Magnesium stearate (1% of lactose)	3.25
Tablet wt., 360.75 mg.	
Spray-Dried Lactose	325.0
Disintegrant (15% of lactose)	48.75
Magnesium stearate (1% of lactose)	3.25
Tablet wt., 377.0 mg.	

TABLE III.—ORDER OF EFFECTIVENESS

15% 120°F.	15% 100°F.	15%, R.T.
Cornstarch	Cornstarch	Cornstarch
Avicel	Avicel	BW-200
BW-100	$CaSO_4$	BW-100
Natrasol	BW-100	$CaSO_4$
$CaSO_4$	BW-200	Avicel
BW-200	Natrasol	Natrasol
CMC	CMC	CMC
10%, 120°F.	**10%, 100°F.**	**10%, R.T.**
Cornstarch	Cornstarch	Cornstarch
Natrasol	Avicel	Avicel
Avicel	Natrasol	$CaSO_4$
BW-100	$CaSO_4$	Natrasol
$CaSO_4$	BW-100	BW-100
BW-200	BW-200	BW-200
CMC	CMC	CMC
5% 120°F.	**5%, 100°F.**	**5%, R.T.**
Natrasol	Natrasol	Natrasol
Cornstarch	Avicel	Cornstarch
Avicel	Cornstarch	Avicel
$CaSO_4$	$CaSO_4$	$CaSO_4$
BW-200	BW-200	BW-100
BW-100	BW-100	BW-200
CMC	CMC	CMC

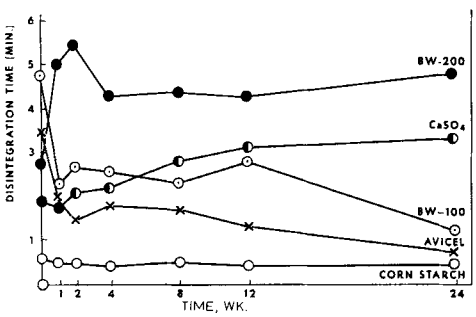

Fig. 1.—Typical disintegration curves for five disintegrants at 15% concentration over a period of 24 weeks at 120°F.

Two thousand tablets were prepared for each formula. The spray-dried lactose and disintegrant were mixed in a Hobart mixer, model N-50, at speed No. 1 for 10 min. The lubricant then was added and mixed for an additional 2 min. The tablets were compressed on a Colton single rotary (240-33) using 13/32 standard concave punches, at 25 r.p.m. or 400 tpm.

All samples were checked initially for hardness and disintegration. They then were placed in bottles containing approximately 200 tablets each and stored at room temperature, 100°F., and 120°F. The samples were rechecked at intervals of 1 and 2 weeks and 1, 2, 3, and 6 months. Hardness was determined with a Pfizer hand model hardness tester. Disintegration was performed according to the U.S.P. method for tablet disintegration.

RESULTS AND DISCUSSION

The most rapid disintegration was achieved with cornstarch at concentrations of 10 and 15%, regardless of storage temperature; while Natrasol gave the best disintegration at the 5% level. The order of disintegrant effectiveness is shown in Table III.

In attempting to evaluate results, the authors took into consideration that many products remain unsold for several months, occasionally years. Therefore, a high initial or 1-week disintegration value would not necessarily rule out a disintegrant if, say, 1 to 6 month values were good. Therefore, the authors felt that the results from 1 to 6 months might carry more weight than those from initial to 2 weeks.

Most of the disintegrants gave their best results at a concentration of 15%. Exceptions were: (*a*) Avicel which had its best disintegration at a concentration of 10%. This was, however, only slightly better than the 15% level. (*b*) Natrasol, which gave its best disintegration at a 5% concentration.

It also was noted that the storage temperature greatly influenced the rate of disintegration. In the majority of cases, those samples stored at 120° F. disintegrated more rapidly than their counterparts stored at the other temperatures.

Figure 1 shows typical disintegration curves for five of the disintegrants in the study at 15% concentration and 120°F. The carboxymethylcellulose is omitted, because after the first week, disintegration times were over 30 min., which was the cut-off point in the study. (Disintegration times over 30 min. were not pursued but merely recorded as >30 min.)

Natrasol is not depicted here because it went over 30 min. during the first 2 weeks. However, Table IV shows what changes did occur with Natrasol.

It can be seen readily that, except for the first two retest periods, Natrasol disintegration is quite good.

Some interesting and rather unexpected results were obtained from the calcium sulfate granulation (79.15% dihydrate). This material was developed to act as an excipient for direct compression. In

TABLE IV.—NATRASOL DISINTEGRATION—15% AT 120°F.

	Time, min.
Initial	5.5
1 wk.	>30
2 wk.	>30
1 mo.	3.9
2 mo.	0.48
3 mo.	0.44
6 mo.	0.6

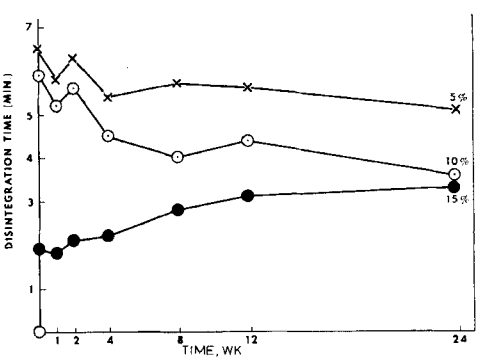

Fig. 2.—Disintegration curves with various concentrations of calcium sulfate granulation over a period of 24 weeks at 120°F.

this study, however, it was treated as a disintegrant and incorporated into another excipient—namely, spray-dried lactose. Considering the nature and intended use of this material, surprisingly it proved to be quite an effective disintegrant (Fig. 2).

In most cases, maximum hardness was reached in 1 to 2 months, then from 3 to 6 months either decreased or showed no change. Natrasol was the exception, as it appeared to increase in hardness for almost every retest period up to 6 months, where then it showed some decrease.

The average hardness values for the $CaSO_4$ granulation were higher than the other disintegrants over the 6-month test period. Natrasol, again somewhat of an exception, had the highest single value at the 3-month test period (15%, 120°F.) of 6.4 Kg., an increase of more than double over its initial value.

SUMMARY AND CONCLUSIONS

1. The majority of the disintegrating agents, when incorporated in a soluble system, seemed to provide the most rapid disintegration at concentrations of 15% and a storage temperature of 120°F.

2. Corn starch, as usual, was the best disintegrant and produced the least variation in disintegration time.

3. $CaSO_4$ granulation, an innovation here because of its more versatile nature (disintegrant and excipient) should be considered and investigated as a standard formula ingredient for future work and not as an exotic to be tried as a last resort.

4. Hardness results appeared to be inconclusive, with the possible exception of $CaSO_4$ granulation which, in general, produced the hardest tablets.

5. Over the 6-month period, a trend toward decreasing disintegration times was effected by the majority of the disintegrants studied. This appears to be contrary to results of wet granulated systems, which usually demonstrate increasing disintegration times with aging.

REFERENCES

(1) Kwan, K. C., Swart, F. O., and Mattocks, A. M., THIS JOURNAL, **46**, 236(1957).
(2) Firouzabadian, A., and Huyck, C. L., *ibid.*, **43**, 248 (1954).
(3) Holstius, E. A., and DeKay, H. G., *ibid.*, **41**, 505 (1952).
(4) Strickland, W. A., Jr., *et al.*, *ibid.*, **45**, 51(1956).
(5) Nair, A. D., and Bhatia, V. M., *ibid.*, **46**, 131(1957).
(6) Gross, H. M., and Becker, G. H., *ibid.*, **41**, 157(1952).
(7) Burlinson, H., and Pickering, C., *J. Pharm. Pharmacol.*, **2**, 630(1950).
(8) Berry, H., *ibid.*, **12**, 501(1939).

Preparation and Stability of Glyceryl Trinitrate Sublingual Tablets Prepared by Direct Compression

By M. DAVID RICHMAN*, C. DAVID FOX*, and RALPH F. SHANGRAW

Tablets of glyceryl trinitrate were prepared by direct compression employing microcrystalline cellulose. These tablets were nonfriable and exhibited sublingual availability comparable to commercially available hypodermic tablets. Compressed tablets of microcrystalline cellulose showed only slight loss of glyceryl trinitrate at 50° when compared to commercial hypodermic tablets which lost up to 95 per cent. Glyceryl trinitrate formulated in a directly compressed sublingual tablet of microcrystalline cellulose presents an aesthetic stable dosage form which is a marked improvement over presently available glyceryl trinitrate dosage forms.

IN SPITE OF the many advances in medicinal chemistry and pharmaceutical technology, the sublingual administration of glyceryl trinitrate by means of hypodermic tablets remains the popular and effective treatment for acute attacks of angina pectoris. Although glyceryl trinitrate has proven, by extent of use and therapeutic action, to be the drug of choice in such conditions, there has been no appreciable progress in the pharmaceutics involved in the dosage form. It would seem that this drug could be formulated into a stable, nonfragile tablet which would release the active ingredient rapidly and surmount most of the pharmaceutical disadvantages inherent in the present commercial hypodermic tablet. Although hypodermic tablets commonly are employed for sublingual administration of glyceryl trinitrate, the choice is based solely on rapidity of dissolution. They are not intended for the preparation of parenteral solutions. Actually the need for hypodermic tablets for the preparation of solutions for injection has been virtually eliminated by technological advances in sterile parenteral preparations in unit dosage forms.

The apparent disadvantages of hypodermic tablets for the sublingual administration of glyceryl trinitrate may be summarized as follows: (*a*) instability of glyceryl trinitrate in hypodermic tablets, (*b*) appreciable friability of such tablets, (*c*) diminutive size of the tablets and difficulty in handling, (*d*) slow and antiquated production methods, (*e*) use of hydro-alcoholic excipients in molding formulations, and (*f*) tablet-to-tablet variation in weight and potency.

A discussion of some of these aforementioned

Received August 3, 1964, from the School of Pharmacy, University of Maryland, Baltimore.
Accepted for publication November 2, 1964.
Presented to the Scientific Section, A.PH.A., New York City meeting, August 1964.
* Recipients of Lunsford Richardson Pharmacy Awards.