Development of a Stable Sublingual Nitroglycerin Tablet II: Formulation and Evaluation of Tablets Containing Povidone

HO-LEUNG FUNG, S. K. YAP, and C. T. RHODES ˣ

Abstract □ Stable and pharmaceutically elegant sublingual nitroglycerin tablets were formulated using povidone to retard volatilization of the drug. Formulation and processing variables were investigated to produce an acceptable product. A blend of two grades of povidone, of different degrees of cross-linkage and water solubility, provided stable tablets which exhibited rapid disintegration. Directly compressed sublingual tablets made in this study retained over 80% of the initial nitroglycerin when exposed to the atmosphere at room temperature for 2 months. The direct compression tablets are of good appearance and low friability, and the formulation is readily compressed without problems. An interesting relationship among the hardness, disintegration time, and compaction pressure is described.

Keyphrases □ Nitroglycerin—sublingual tablets containing povidone, formulation and processing variables investigated, effect of compaction pressure on hardness and disintegration time □ Povidone—two grades used in sublingual nitroglycerin tablets, formulation and processing variables investigated □ Dosage forms—sublingual nitroglycerin tablets containing povidone, formulation and processing variables investigated

Recently, studies of the interaction between a number of pharmaceutically acceptable macromolecules and nitroglycerin were reported (1). Povidone substantially reduced the loss of nitroglycerin from test powder mixtures. Thus, it was felt that the design of nitroglycerin dosage forms containing povidone merited a full investigation.

When this study was initiated, molded nitroglycerin tablets were the most common sublingual dosage form used to provide rapid relief from the symptoms of angina. However, it seemed that there would be considerable advantages in producing directly compressed sublingual nitroglycerin tablets. In particular, the advantages of the direct compression process justified an attempt to exploit this technique. Some work indicated that there is potential for directly compressed nitroglycerin tablet formulations (2).

In this paper, formulation studies resulting in the development of stabilized nitroglycerin sublingual tablets are reported. These tablets are stable under most rigorous storage conditions, disintegrate rapidly, and compare favorably with existing commercial tablets.

EXPERIMENTAL

Materials—Two grades of povidone, designated types I[1] and II[2] (type I has a much lower degree of cross-linkage and an appreciably greater water solubility than type II), sucrose[3], corn starch[4], sodium starch glycolate[5], lactose USP[6], magnesium stearate[3], and a nitroglycerin–lactose mixture[7] containing 10% (w/w) of nitroglycerin were used without further purification.

Method—Molded tablets were prepared by dry mixing the component powders and then adding 1 ml of 50% (v/v) aqueous ethanol/12 g of powder as granulating fluid. The mass was then molded, and the formed tablets were allowed to dry at room temperature overnight.

The directly compressed tablets were prepared by a single-punch tablet press[8] with 5-cm beveled punches. The tablet components were mixed well by quartering. Tablets were prepared at seven different arbitrary compaction pressures from P_1, lowest, to P_7, highest. They were then evaluated for disintegration time using the USP apparatus. Friability was determined by a circular friabulator[9], 10 tablets being rotated for 15 min after a preliminary dedusting. Determination of weight loss after the operation allowed estimation of percentage friability. Tablet hardness values were measured using an electric hardness tester[10].

Physical stability of the tablets, in terms of nitroglycerin loss, was evaluated by storing samples of 40 tablets in open petri dishes at room temperature. The dishes were placed over 0.61 m (2 ft) apart to prevent migration of nitroglycerin between samples (1, 3, 4). The nitroglycerin content of the tablets was determined as a function of time using the assay technique described previously (5). For comparison purposes, two commercial brands of nitroglycerin tablets, Brands A[11] and B[12], were included in this study.

RESULTS AND DISCUSSION

Previously, it was shown that concentrations between 5 and 15% of povidone type I had a substantial stabilizing effect on nitroglycerin (1). Figure 1 shows the effect of varying the concentration of I on the hardness and disintegration time of molded sublingual nitroglycerin tablets containing 5% sucrose and lactose USP as the diluent. Increasing the proportion of I increased the hardness of the molded tablets until the concentration was about 10% (w/w),

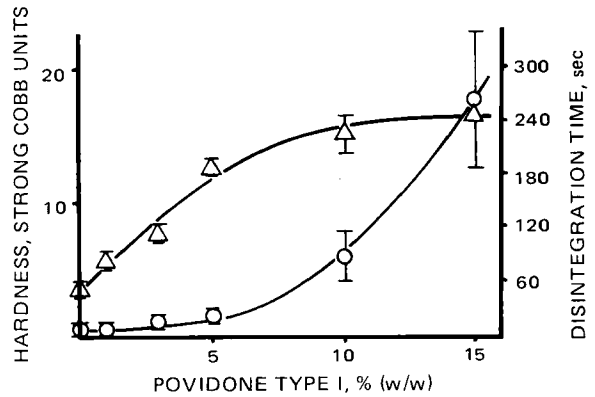

Figure 1—*Hardness (△) and disintegration time (○) of molded sublingual nitroglycerin tablets containing different proportions of povidone type I. Each data point represents the mean and standard deviation of six determinations.*

[1] Plasdone K-29-32, GAF Corp., New York, NY 10020
[2] Plasdone XL, GAF Corp., New York, NY 10020
[3] Fisher Scientific, Fair Lawn, NJ 07410
[4] Argo, Best Foods, Inc., Englewood Cliffs, NJ 07410
[5] Primojel K, Edward Mendell Co., Jefferson Valley, NY 10535
[6] Mallinckrodt Chemical Works, St. Louis, MO 63160
[7] ICI America, Tamaqua, PA 18252
[8] Erweka type TA3, Chemical and Pharmaceutical Co., New York, NY 10013
[9] Roche friabulator, Chemical and Pharmaceutical Co., New York, NY 10013
[10] Strong Cobb model PT102, J. H. Delmar and Sons, Chicago, IL 60625
[11] NitroPRN, 0.6 mg, Lot 4583044B, Warner-Chilcott, Morris Plains, NJ 07950
[12] Nitrostat, 0.6 mg, Lot MA153, Parke-Davis, Detroit, MI 48232

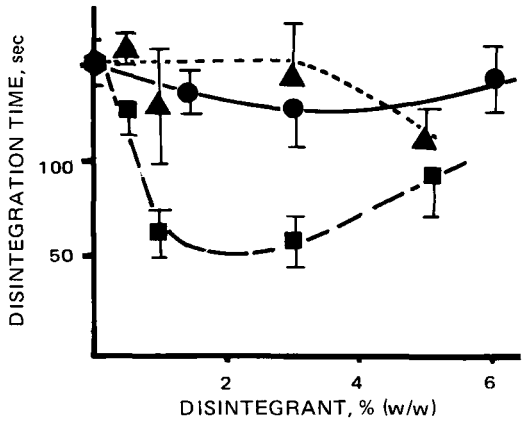

Figure 2—*Disintegration characteristics of molded sublingual nitroglycerin tablets containing 10% povidone type I and different concentrations of the disintegrant corn starch (●), sodium starch glycolate (▲), and povidone type II (■). Each data point represents the mean and standard deviation of six determinations.*

above which little change in hardness was observed. Conversely, an increase in the I concentration up to about 8% (w/w) had little effect on the disintegration time of the molded tablets. However, a quite abrupt increase in the disintegration time was detected above this value.

To retain the stabilizing effect of I without excessively long disintegration times, the percentage of this component was fixed at 10% (w/w). Although I did not have an excessive binding effect at the 10% level, it was still necessary to add a disintegrant. Following a preliminary screening, three materials—corn starch, sodium starch glycolate, and povidone type II (6)—were selected for detailed study. Figure 2 shows disintegration times for the molded tablets [containing 10% (w/w) I] as a function of disintegrant concentrations. Obviously, II offered the greater advantage in terms of diminution of disintegration time. Another advantage of including this material in the formulation was that it had a stabilizing action on nitroglycerin, albeit slightly less than that shown by I (Table I).

The formula (Formula I) selected for the molded tablet was:

nitroglycerin–lactose powder	*q.s.*
sucrose	5.0%
povidone type I	10.0%
povidone type II	2.0%
lactose monohydrate USP	to 100.0%

The poor weight uniformity, difficulty of preparation, and generally poor physical properties of these molded tablets stimulated study of direct compression tablets. The studies of the molded tablets had shown that the combination of povidone types I and II offers unique advantages in the formulation of nitroglycerin tablets. Therefore, this finding was exploited for the direct compression tablets. Of course, with a compressed tablet, the additional variable of compaction force can affect hardness–disintegration time relationships.

Figure 3 shows the effect of varying compaction pressure and percentage of II on the hardness and disintegration time of tablets containing 10% (w/w) I, 2% magnesium stearate, and lactose as the diluent. The effect of altering the concentration of II between 3 and 8% on disintegration time apparently was related to the effect of this substance on tablet hardness. With one exception, the data

Table I—Stability of Nitroglycerin in Lactose Powder Containing Povidone Type II upon Exposure to the Atmosphere at Room Temperature

	Percent Nitroglycerin Remaining in Powder in		
	7 Days	14 Days	28 Days
Control	37	6	5
With 10% (w/w) povidone type II	87	80	70

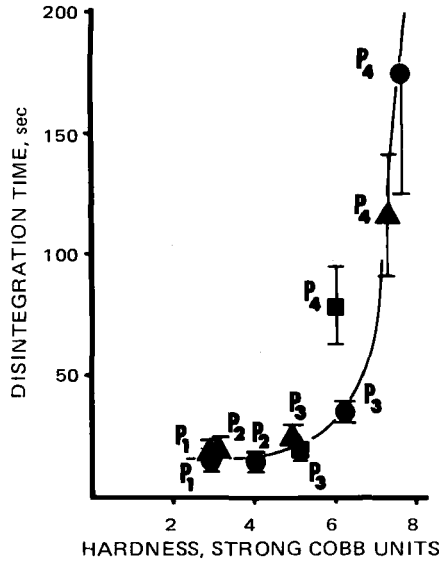

Figure 3—*Hardness and disintegration time of direct compression sublingual tablets containing 10% (w/w) povidone type I and 3% (●), 5% (▲), and 8% (■) of povidone type II produced under different compaction pressures. The* P *values indicate different compaction pressure from* P_1, *lowest, to* P_4, *highest.*

points derived from different concentrations of II and different compaction pressures fell on the same smooth curve. A concentration of 10% II was included in the selected formula. However, since the disintegration times of tablets containing 10% (w/w) I and 10% (w/w) II were still somewhat longer than desirable, another disintegrant was added to the formulation. Sodium starch glycolate, a water-soluble starch derivative having considerable potential in direct compression systems, was chosen for this purpose (7).

The selected direct compression formula (Formula II) was:

nitroglycerin–lactose powder	*q.s.*
sodium starch glycolate	1.0%
magnesium stearate	2.0%
povidone type I	10.0%
povidone type II	10.0%
lactose monohydrate USP	to 100.0%

which compresses to give tablets between 3.0 and 4.5 Strong Cobb hardness units.

The tablets prepared using Formula II have an elegant appearance, having a smooth, clean, white surface. The formula compresses readily; no evidence of "capping," "sticking," or other compression problems was detected. The excellent weight uniformity is indicative of good flow properties of the formulation (Table II). It is possible to reduce the concentration of magnesium stearate and still have good lubrication; reduction in the concentration of this component further decreases disintegration times. Of course, the final selection of optimum processing and formulation variables must depend on the type of tablet press used as well as the scale of production. In particular, the shorter dwell times on a rotary press might necessitate some minor changes. However, no major change is required.

Figure 4 shows the effect of variation in compaction pressure on the hardness and disintegration time of the compressed tablets. It is obvious that the disintegration time of the tablets remained essentially constant at less than 30 sec as long as the compaction pressure used produced tablet hardness of 5 Strong Cobb units or less. A further increase in compaction pressure caused only a slight increase in hardness but an exponential increase in the disintegration time of the tablets. In practice, tablet hardness of 3–4 Strong Cobb units is sufficient for sublingual tablets. Hence, this peculiar physical characteristic of povidone-stabilized direct compression nitroglycerin tablets is not a major quality control problem.

The interesting disintegration characteristics of direct compression nitroglycerin sublingual tablets containing povidone can, perhaps, be explained as follows. The disintegration of a tablet in a USP disintegration apparatus can be considered as consisting of two processes: bulk disintegration and surface erosion. In bulk dis-

Table II—Stability, Hardness, Disintegration Time, Friability, and Weight Uniformity of Brands A and B and Formula II

	Brand A (Compressed)	Brand B (Molded)	Formula II (Compressed)
Hardness, Strong Cobb units[a], mean (*SD*)	3.0 (0.3)	2.4 (0.2)	2.7 (0.4)
Disintegration time, sec[a], mean (*SD*)	7 (1)	23 (4)	14 (1)
Friability, %	1.2	6.7	1.3
Weight uniformity[b], mg, mean (*SD*)	33.1 (0.2)	35.6 (0.8)	77.2 (0.4)
Water-insoluble ingredients, % (means of three determinations)	60	0	12

[a] Determination of six tablets. [b] Determination of 10 tablets.

integration, capillary action or other mechanisms draw water into the tablet through pores, and subsequent swelling of the disintegrant ruptures the tablet structure. The fact that the disintegration time is essentially independent of compaction pressures between hardness values of 2–5 Strong Cobb units indicates that in such systems the rate of entry of water into the tablet is not rate determining and that bulk disintegration predominates in the overall disintegration of the tablet.

However, as compaction pressure is increased, tablet porosity decreases. Above a hardness of 5 units, the very different behavior may be due to reduction of tablet porosity beyond the critical value at which the reduction of the rate of water entry into the tablet diminishes the role of bulk disintegration in the total disintegration of the tablet. Therefore, as compaction pressure is increased, bulk disintegration decreases substantially and the slower surface erosion process predominates in the overall tablet disintegration. Detailed evaluation of compaction pressure and porosity would be required to elucidate fully the reasons for this interesting behavior.

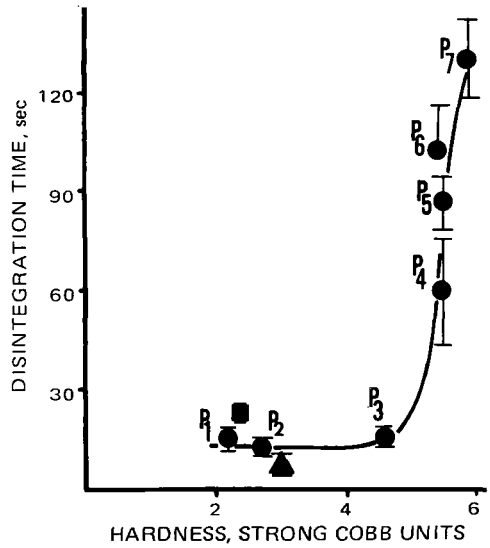

Figure 4—*Hardness and disintegration time of nitroglycerin sublingual tablets. Key: ●, Formula II; ▲, Brand A; and ■, Brand B. The* P *values indicate different compaction pressures. Each data point represents the mean and standard deviation of six determinations.*

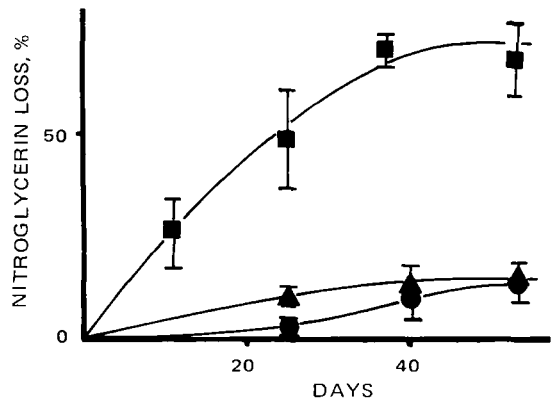

Figure 5—*Loss of nitroglycerin from Formula II (●), Brand A (▲), and Brand B (●) on exposure to the atmosphere on open petri dishes at room temperature. Each data point represents the mean and standard deviation of six single-tablet assays.*

The present authors previously reported (1) extraction experiments, which indicate that the formulation components used in this study are unlikely to affect biological availability adversely. Detailed clinical studies of nitroglycerin products, both tablets and ointments, would be useful.

Results of the comparative evaluations of the compressed tablets described in this study and commercially available tablets (Brand A, compressed, and Brand B, molded) are shown in Table II and Fig. 5. Even under the quite thorough test used in this investigation, the tablets prepared in this study and Brand A commercial tablets showed a high degree of stability. The test used was far more rigorous than one might expect in normal use.

It can be seen from Table II that the direct compression tablets described in this study compared favorably with Brands A and B in terms of weight uniformity and disintegration time. Table II also contains estimates of the percentage of water-insoluble ingredients in each of the three types of tablets. Estimates were obtained by shaking 100 tablets vigorously for 30 min with 30 ml of distilled water, filtering, and then weighing the residues. Brand B appears to be comprised entirely of water-soluble components; the product reported in this study had about 12% of water-insoluble material, while Brand A had approximately 60% (w/w) water-insoluble material. All three types of tablets had an acceptable "mouth feel," but some formulators might feel that 60% water-insoluble material in a sublingual tablet is high.

From the data presented, it is apparent that the direct compression tablet formulation reported herein compares very favorably with other recently introduced formulations which were developed to overcome the problem of nitroglycerin loss.

REFERENCES

(1) H.-L. Fung, S. K. Yap, and C. T. Rhodes, *J. Pharm. Sci.*, **63**, 1810(1974).

(2) M. D. Richman, C. D. Fox, and R. F. Shangraw, *ibid.*, **54**, 447(1965).

(3) S. A. Fusari, *ibid.*, **62**, 122(1973).

(4) *Ibid.*, **62**, 2012(1973).

(5) H.-L. Fung, P. Dalecki, E. Tse, and C. T. Rhodes, *J. Pharm. Sci.*, **62**, 696(1973).

(6) S. K. Kornblum and S. B. Stoopak, *ibid.*, **62**, 43(1973).

(7) K. A. Khan and C. T. Rhodes, *Pharm. Acta Helv.*, **47**, 153(1972).

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