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.

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

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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

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points appears warranted at this time. The supposition of decreasing potency in hypodermic tablets due to the volatilization of the glyceryl trinitrate is accepted universally (1). However, a literature review on the tableting of glyceryl trinitrate and the stability of such products has shown that the amount of work is extremely limited and there is little to substantiate this premise (2–4).

The excessive friability of hypodermic tablets as compared to compressed tablets is well known. This is of particular importance in the case of glyceryl trinitrate, which has an extremely small dose. If it can be assumed that the amount of active ingredient is so small that it would be soluble in the hydro-alcoholic excipient utilized in the manufacture of molded hypodermic tablets, then the glyceryl trinitrate may well migrate to the surface during the drying process. The active ingredient would then be concentrated on the surface facilitating loss by means of volatilization, as well as a disproportionate loss of potency due to erosion or chipping. This would help to explain the supposed decrease in potency when such tablets are carried about by a patient in a pocket or handbag. It is a fact that these tablets are difficult to handle during the consternation of an anginal attack and that the patient may inadvertently pour more than one tablet into his hand and place them into the mouth at one time. Testimonies as to apparent potency loss of tablets under such conditions of stress are worthless.

A skilled operator, using standard hypodermic molds of 200-tablet capacity, can, on the average, produce 10,000 to 12,000 hypodermic tablets per 8-hr. day. Machines are available for making tablet triturates at a much higher rate, but they lack flexibility for other types of products and the decline of the use of molded tablets makes such machines economically unfeasible for most pharmaceutical companies. If a sublingual formulation of glyceryl trinitrate were available that could be compressed into tablets on a standard 39-station double-rotary tablet press, the production rate per 8-hr. day would be approximately 1 million tablets, or an increase of 100-fold over the manual production method. Thus, the production of sublingual tablets on a rotary press would appear to offer a substantial economic advantage. This would be particularly true if no pregranulation or slugging were required.

However, if the preparation of compressed tablets is considered using conventional wet granulation procedures, certain major disadvantages are evident. The required binder and lubricant in all probability would impede tablet disintegration markedly. The use of liquid granulating agents would necessitate a drying period and, as in the case of molded tablets, migration of the drug could occur. Stability of the glyceryl trinitrate in the presence of the granulating solution also would have to be determined. The economic factors of time, power requirements for drying, and the need for granulating equipment also are important. Finally, the possibility of explosion under compression cannot be dismissed without consideration.

The development of microcrystalline cellulose[1] and its application as a tableting agent in direct compression (5–7) suggested its possible use in the preparation of sublingual tablets of glyceryl trinitrate. The following properties are characteristic of microcrystalline cellulose: (*a*) capable of direct compression without addition of binders, (*b*) good flow properties, (*c*) high adsorption capacity, (*d*) imparts low friability to finished tablets, (*e*) promotes fast tablet disintegration, and (*f*) enhances rapid drug availability from tablets.

On the basis of these properties, it would seem that tablets of glyceryl trinitrate in microcrystalline cellulose could be produced by direct compression without subjecting the mixture to fluids such as alcohol or water, heat, or additives such as binders and lubricants. These tablets would be hard, easily handled, and display rapid disintegration and drug availability. The process would be quite economical since the preparation involves only a minimum number of operations. The possibility that glyceryl trinitrate in the usual therapeutic dosage might explode under compression has been stated to be nonexistent (3). In addition, dispensing tablets of much higher strengths have been prepared previously commercially by means of compression.

The over-all objectives of the investigation may be summarized as follows:

(*a*) The preparation of nonfriable tablets of glyceryl trinitrate, by direct compression, which will release the active ingredient promptly.

(*b*) The study of the stability of such tablets as compared with commercial hypodermic tablets of glyceryl trinitrate.

(*c*) The comparison of *in vivo* action of molded hypodermic and compressed microcrystalline cellulose tablets.

EXPERIMENTAL

Manufacture of Tablets.—So that a meaningful investigation could be carried out, it was necessary to utilize a suitable analytical procedure to assay

[1] Marketed as Avicel by the American Viscose Co., Marcus Hook, Pa.

small quantities of glyceryl trinitrate. After a review of other analytical procedures (8, 9), the method of Bell (10) was selected. The sensitivity of the assay and the accuracy obtainable contributed in a high degree to the success of the experimental work. The method involves the alkaline hydrolysis of glyceryl trinitrate and the subsequent determination of the nitrate by diazotization and coupling. The use of strontium hydroxide as the hydrolyzing agent probably results in the formation of the strontium salt of lactose, which is of sufficient stability to remove the lactose from the field of interference. The reaction mixture provides a pink-colored solution conforming to Beer's law, which is assayed spectrophotometrically at 550 mμ. This method is rapid, suitable for single tablet analyses, precise, and accurate, and can be conducted with readily available equipment.

By means of this assay procedure, Bell was able to show appreciable differences between the amounts of active ingredient in individual hypodermic tablets of commercially available products.

An attempt was made to prepare tablets by mixing 10% of a commercial lactose–glyceryl trinitrate mixture[2] with 90% microcrystalline cellulose. This mixture failed to exhibit suitable flow properties. The addition of 1% glidant[3] produced a free-flowing powder which could be tableted. However, since the glidant would contribute another variable to the experiment, it was decided to add directly pure glyceryl trinitrate to the microcrystalline cellulose. The glyceryl trinitrate used in this study was obtained by extraction of the lactose–glyceryl trinitrate mixture with acetone. This method proved to be a much simpler process than synthesizing the glyceryl trinitrate and provided a product of equal purity.

Approximately 45 Gm. of the 10% lactose–glyceryl trinitrate mixture was extracted ten times with 50-ml. portions of acetone. Each portion was passed through hardened filter paper in a Büchner funnel. As a precautionary measure the resultant acetone filtrate, which contained approximately 1% glyceryl trinitrate, was stored in the refrigerator until used. Acetone was selected as the solvent vehicle in preference to absolute ethyl alcohol to eliminate any possibility of transesterification which can occur in alcoholic solution.

By adding the acetone solution directly to the microcrystalline cellulose, it was hoped that the nitroglycerin would hydrogen bond with the cellulose, thus decreasing the possibility of volatilization. Previous studies with other drugs have shown that even if hydrogen bonding does occur, the active ingredients are readily available when the microcrystalline cellulose tablets are placed in water (7). Because of the great importance of obtaining uniform distribution of the glyceryl trinitrate, great care was taken during blending to assure homogeneity.

Four-hundred grams of microcrystalline cellulose was placed in a Kitchen mixer, model K5-A and the glyceryl trinitrate–acetone solution added slowly by means of a pipet, with the mixer operating at its lowest speed. About 60 min. were required for the addition of 500 ml. of solution. The microcrystalline cellulose agglomerated somewhat during the blending process but assumed its original free-flowing properties as the acetone evaporated. To insure complete removal of the solvent, the mixer was operated for 45 min. after the solution had been added, and the powder subsequently was spread onto a tray and carefully agitated with a spatula until there was no perceptible odor of acetone. The blended mixture was stored in a desiccator at ambient temperature.

[2] Provided as 10% nitroglycerin–90% β-lactose w/w mixture, lot CC 21B59, E. I. du Pont de Nemours and Co., Inc., Wilmington, Del.

[3] Provided as Cab-O-Sil by G. Cabot and Co., Boston, Mass.

TABLE I.—PHYSICAL CHARACTERISTICS OF COMMERCIAL GLYCERYL TRINITRATE TABLETS

Co.	Av. Wt., mg.	Av. Wt. Variation, mg.	Diameter, in.	Thickness, in.
XL	33	±1.80	0.130	0.100
XP	31	±2.25	0.160	0.095
XB	33	±1.50	0.167	0.085

Tablets containing 0.5 mg. of glyceryl trinitrate were compressed directly on a Colton model 216 rotary press using $^{7}/_{32}$-in. flatface tooling. No additives such as lubricants, glidants, or binders were needed. The tablet machine was run at a slow speed to give maximum uniformity in die fill and minimum tablet weight variation. The following figures are based on averages of 20 tablets: weight, 46 mg.; average weight variation, 0.9 mg.; diameter, 0.220 in.; thickness, 0.086 in.; hardness (Strong-Cobb), 3.5.

Stability.—An experiment was designed to compare the stability of the compressed tablets with hypodermic tablets manufactured by three different pharmaceutical companies. These commercial products were purchased locally in units of 1000 tablets. They were labeled as containing 1/150 gr. (0.4 mg.) of glyceryl trinitrate per tablet in a base consisting of lactose and sucrose. Twenty tablets from each manufacturer were examined and found to exhibit the characteristics shown in Table I.

Three 200-tablet samples of each of the commercial hypodermic tablets as well as the compressed microcrystalline cellulose tablets were placed into separate 5-dram green screw-capped vials. The sample vials were divided into three groups, with each group containing a sample from each manufacturer. One group was placed into a constant-temperature oven at 50°, a second into another constant-temperature oven at 37°, and a third into a desiccator at room temperature. The tablets were removed daily from each vial, spread out onto a glass plate for 2 min., and then returned to their respective vials. This procedure was believed to permit adequate opportunity for volatilization, while at the same time simulating to some extent actual use conditions. Samples of tablets were assayed periodically. Five assays of four tablets each were carried out, and the mean of these assays represents the reported tablet potency. The results of the 50° study may be seen in Table II and Fig. 1. Since there was no apparent loss at 50° for the first several weeks, the 37° samples were not checked until 7 weeks had elapsed. The results of the assays of the 37° study may be seen in Table III. There was no apparent loss of glyceryl trinitrate from any of the samples maintained at room temperature.

TABLE II.—SUMMARY OF ASSAY RESULTS OF GLYCERYL TRINITRATE TABLETS AT 50°C.

Time, Days	Batch	Mean Assay of Four Tablets, mg./Tablet					Av., mg./Tablet
Initial Assay	MCC–GTN[a]	0.54	0.53	0.52	0.54	0.54	0.53
	XL	0.40	0.40	0.41	0.42	0.45	0.42
	XP	0.47	0.42	0.44	0.45	0.48	0.45
	XB	0.40	0.47	0.38	0.43	0.35	0.41
11	MCC–GTN	0.48	0.50	0.52	0.50	0.48	0.50
	XL	0.40	0.42	0.39	0.40	0.39	0.40
	XP	0.42	0.43	0.44	0.44	0.42	0.43
	XB	0.42	0.42	0.42	0.40	0.39	0.41
21	MCC–GTN	0.47	0.49	0.47	0.49	0.49	0.48
	XL	0.41	0.41	0.40	0.41	0.41	0.41
	XP	0.40	0.41	0.40	0.37	0.36	0.39
	XB	0.36	0.36	0.35	0.31	0.32	0.34
34	MCC–GTN	0.47	0.46	0.47	0.48	0.46	0.47
	XL	0.34	0.38	0.37	0.36	0.36	0.36
	XP	0.30	0.27	0.29	0.30	0.29	0.29
	XB	0.33	0.27	0.28	0.28	0.28	0.29
64	MCC–GTN	0.47	0.45	0.46	0.46	0.46	0.46
	XL	0.16	0.15	0.15	0.16	0.16	0.16
	XP	0.08	0.07	0.08	0.09	0.08	0.08
	XB	0.02	0.02	0.02	0.03	0.02	0.02

[a] MCC–GTN: Microcrystalline cellulose–glyceryl trinitrate, XL, XP, XB: commercial hypodermic tablets.

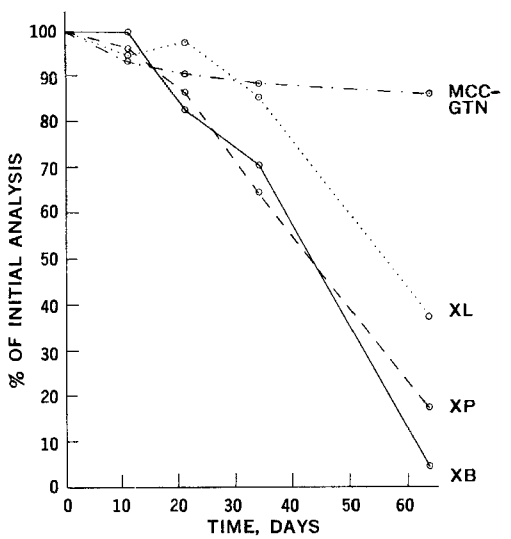

Fig. 1.—The influence of storage at 50° on stability of glyceryl trinitrate tablets.

To point up the difference in friability between the experimental compressed and commercial molded tablets, both were evaluated in a Roche friabilator using the standard procedure (11). The microcrystalline cellulose tablets exhibited an 0.8% friability compared to 2.3, 2.2, and 1.4% for samples XL, XP, and XB, respectively.

Formulation.—Although patients who routinely use sublingual glyceryl trinitrate do not complain about it, there is no question that it does produce a burning sensation when applied to mucous membranes. To minimize this effect and to overcome partially the "flourlike" mouth feel of the insoluble microcrystalline cellulose, a slight modification in the tablet formulation was made. The following proposed formulation will improve patient acceptability, while at the same time maintaining direct compression capability:

	w/w
Flavor (spray dried or powdered)	1%
Sodium cyclamate	1%
Mannitol	3–8%
Microcrystalline cellulose	90%
Active ingredient	up to 5%

TABLE III.—SUMMARY OF ASSAY RESULTS OF GLYCERYL TRINITRATE TABLETS AT 37°C.

Time, Days	Batch	Mean Assay of Four Tablets, mg./Tablet					Av., mg./Tablet
Initial Assay	MCC–GTN[a]	0.54	0.53	0.52	0.54	0.54	0.53
	XL	0.40	0.40	0.41	0.42	0.45	0.42
	XP	0.47	0.42	0.44	0.45	0.48	0.45
	XB	0.40	0.47	0.38	0.43	0.35	0.41
53	MCC–GTN	0.55	0.55	0.55	0.56	0.56	0.55
	XL	0.42	0.43	0.44	0.44	0.44	0.43
	XP	0.45	0.42	0.45	0.45	0.44	0.44
	XB	0.37	0.44	0.42	0.47	0.47	0.43
64	MCC–GTN	0.50	0.51	0.51	0.50	0.50	0.50
	XL	0.37	0.26	0.28	0.33	0.30	0.31
	XP	0.37	0.34	0.31	0.36	0.36	0.36
	XB	0.34	0.37	0.39	0.36	0.37	0.37

[a] MCC–GTN: Microcrystalline cellulose-glyceryl trinitrate, XL, XP, XB: commercial hypodermic tablets.

The far reaching importance of this formulation is the fact that most drugs intended for sublingual administration may be compressed directly with this base provided the dose of the active ingredient does not constitute more than 5% of the total tablet weight.

In Vivo Absorption.—The release of glyceryl trinitrate from hypodermic tablets is dependent on the dissolution of the lactose base, whereas disintegration governs the release from a compressed microcrystalline matrix. In an aqueous environment, both processes occur in approximately 15 sec., and it was felt that an *in vitro* study could not indicate adequately the onset of action or degree of therapeutic response, which are of prime importance in angina therapy with glyceryl trinitrate.

A limited investigation was undertaken in an attempt to find a suitable *in vivo* test which would allow a valid comparison of glyceryl trinitrate availability.

Because glyceryl trinitrate is difficult to evaluate in animals, a study was conducted on five healthy humans, utilizing the Beckman model SM-2 continuous systolic monitor. This instrument continuously records the systolic pressure in a peripheral artery without necessitating an arterial puncture and is simply an adaptation of the common indirect method.

After allowing the instrument to record the normal systolic pressure, each subject was given 0.3 mg. of glyceryl trinitrate in a commercial hypodermic tablet by the sublingual route. Any fall in pressure was noted and the recording continued until the systolic pressure returned to normal. Four hours later this procedure was repeated, except that each subject received 0.3 mg. of glyceryl trinitrate in a compressed tablet of microcrystalline cellulose. Experimental results showed no difference between compressed and molded tablets either as to onset of fall (approximately 2 min.), or extent of fall (approximately 20 mm. Hg). However, the duration of fall was slightly longer (4 min. compared to 2.5 min.) in the case of the nitroglycerin–microcrystalline cellulose tablets.

DISCUSSION

The low friability exhibited by the microcrystalline cellulose–glyceryl trinitrate tablets can be considered a marked improvement over tablets made by molding. Compaction of powders by compression produces tablets which have stronger interparticulate bonds. This enables the tablets to resist fracture and erosion and is especially true of those tablets in which microcrystalline cellulose accounts for most of the tablet weight. The "matchsticklike" bundles of microcrystalline cellulose are easily intermeshed upon slight compression, and the numerous sites for hydrogen bonding found in the molecules enable the finished tablet to exhibit extreme hardness. Furthermore, the ability of water to break these bonds causes microcrystalline cellulose tablets to show exceptionally rapid disintegration.

The results of the stability studies show that decrease in glyceryl trinitrate potency may occur due to volatilization. For the 9-week period studies, this loss was significant only at exaggerated temperature conditions. The commercially available tablets lost as much as 95% of their original strength during this period when stored at 50°. Losses were small initially but increased dramatically after 5 weeks. The excellent stability shown by the microcrystalline cellulose–glyceryl trinitrate tablets can be attributed to the fact that strong hydrogen bonding can occur between the glyceryl trinitrate and the microcrystalline cellulose. The slight loss shown with these tablets is probably due primarily to volatilization from the tablet surface. The smaller losses shown in the 37° studies point up the temperature dependency of the glyceryl trinitrate loss.

Since there were no apparent losses in tablet potency of any of the tablets studied at room temperature, the purported claims of instability of glyceryl trinitrate tablets by patients taking this medication are probably not attributable to the volatility of glyceyl trinitrate. Some loss also may occur through erosion of the tablet surfaces which takes place during the period of portage subsequent to dispensing. This is further substantiated when one considers that the vapor pressure of glyceryl trinitrate, at 20°, is 0.00026 mm. (12). The preparation of glyceryl trinitrate with microcrystalline cellulose by direct compression minimizes loss of potency due to either volatilization or erosion.

SUMMARY AND CONCLUSIONS

Nonfriable tablets of glyceryl trinitrate have been prepared by direct compression employing microcrystalline cellulose as the tablet matrix.

The availability of the active ingredient from such compressed tablets, as shown by a marked lowering of systolic pressure, is rapid, and compares favorably with commercial hypodermic tablets.

Compressed tablets of microcrystalline cellulose show only slight loss of glyceryl trinitrate at 50° as compared to commercial hypodermic tablets which show losses up to 95%.

The volatility of glyceryl trinitrate is not a factor in the stability of hypodermic tablets stored at room temperature.

As a result of this investigation, the authors are of the opinion that the use of 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.

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