Influence of Formulating Factors on Drug Safety of Timed-Release Nitroglycerin Tablets

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Abstract □ A peroral sandwich model tablet with timed release, containing proxyphylline and nitroglycerin, was developed. One layer of the tablet constituted the rapidly disintegrating and dissolving initial phase; the other, the depot phase, was in the form of an insoluble, indigestible skeleton. Amount of drugs in the tablet and their liberation rate constants were based on pharmacokinetic calculations. Upon chewing and masticating a depot tablet, the retard action usually is lost due to an increase of the surface. This problem would not be serious with proxyphylline, which is relatively nontoxic, but could be dangerous or fatal in the case of nitroglycerin. To obtain safety with this product, proxyphylline of the depot phase was incorporated into the pores of an indigestible plastic skeleton of the matrix, and nitroglycerin was dissolved in the plastic particles of the matrix. *In vitro* and *in vivo* experiments proved the loss of depot action for both drugs upon mastication of the tablet, yet the nitroglycerin release was slow enough not to cause unwanted side effects.

Keyphrases □ Nitroglycerin—with proxyphylline, formulating timed-release tablets, absorption □ Timed-release tablets—nitroglycerin and proxyphylline □ Bioavailability—timed-release nitroglycerin tablets □ Drug safety—skeleton matrix depot tablets, nitroglycerin □ Depot tablets—*in vitro* drug availability

In a previous study (1, 2), a proxyphylline peroral dosage form, a two-layer tablet with timed release, was developed. Based on pharmacokinetic calculations (Table I), the biopharmaceutical development of the dosage form was done and verified *in vivo* in man using blood level curves (3, 4).

The purpose of the present research work was to incorporate the short-acting nitroglycerin into this existing preparation. The peroral absorption of nitroglycerin has been and is still questioned. Salter (5) stated that nitroglycerin is not decomposed by the gastric juice, but its rate of absorption is slow. Sollman (6) mentioned that nitroglycerin is more potent when orally (buccally) administered instead of perorally, since by the latter route nitroglycerin is absorbed into the portal circulation and then destroyed by the liver. That nitroglycerin is also perorally absorbed—at least in the rabbit—was shown by Turner (7), Lorenzetti *et al.* (8), and Bogaert *et al.* (9). A study of the bioavailability of nitroglycerin upon peroral administration *versus* buccal administration was, therefore, included in this research.

Table I—Pharmacokinetics of Proxyphylline in a Timed-Release Tablet into Which Nitroglycerin Was to Be Incorporated

Biological half-life	$T_{1/2} = 4.3$ (hr.)
Absorption rate constant	$K_A = 1.3$ (hr.$^{-1}$)
Elimination rate constant	$K_{EL} = 0.163$ (hr.$^{-1}$)
Time to reach peak	$T_P = 2.5$ (hr.)
Therapeutic concentration to maintain for 12 hr.	$B_D = 0.8$ (mg./100 ml.)
Single dose producing desired blood level	$D_B = 0.48$ (g.)
Liberation constant from depot phase	$k_R^1 = 0.4$ (hr.$^{-1}$)
Equation for plasma concentration	$C = 11.5 \cdot e^{-0.163T} - 12.5 \cdot e^{-1.3T}$
Percent absorbed relative to the amount ultimately absorbed	$\frac{A_T}{A}, 100 = CT + K_{EL}TC_{DT}$ Percent after 0.25 hr. = 35.6 0.5 hr. = 45.5 1.0 hr. = 74.4 1.5 hr. = 100.0

Maintenance dose:

$$D_M = \frac{K_{EL} \cdot B_D}{k_R^1} = 0.312 \text{ (g.)}$$

Initial dose:

$$D_I = D_B - D_M \cdot (k_R^1 \cdot T_P) = 0.177 \text{ (g.)}$$

Total dose per tablet:

$$W = D_B - D_M \cdot (k_R^1 \cdot T_P) + \frac{K_{EL} \cdot B_D}{k_R^1} = 0.489 \text{ (g.)}$$

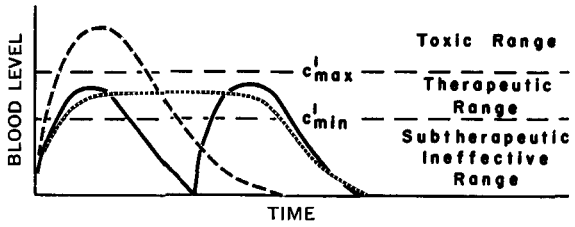

Figure 1—*Schematic blood level curves upon peroral administration. Key: ——, normal single dose; - - -, double single dose; and . . ., dose with timed release.*

In the development of a drug product, one must also consider the safety of the drug. If a drug has a short biological half-life, a dosage form with a matrix that slowly releases the drug is logical. But higher doses have to be given than are usually given in a single dose. If the high dose would be given instantaneously, it could result in toxic blood levels (Fig. 1).

Upon chewing or masticating the previously developed proxyphylline timed-release tablets, the depot effect was lost due to an increase in surface area. This problem is not serious with proxyphylline, which is relatively nontoxic, but it could be dangerous or even fatal with a high dose of nitroglycerin.

EXPERIMENTAL

Materials—Proxyphylline[1] (β-hydroxypropyltheophylline) and nitroglycerin solution[2], 0.1% ethanol, were used as supplied. Ethylcellulose powder[3] of different viscosity grades, 10, 20, and 45 cps., was sieve screened for different particle-size ranges with mean particle sizes of 0.5 and 1.0 mm., respectively. Polyvinyl acetate[4] and a polyamide[5] were screened for different particle-size ranges, and a polyacrylate[6] was sieve screened as mentioned previously. Organic solvents for granulation were of laboratory grade.

[1] Siegfried AG., Zofingen, Switzerland.
[2] Sprengstoff AG., Dottikon, Switzerland.
[3] Ethocel, Dow Chemical Co., Midland, Mich.
[4] Hoechst AG., Frankfurt/Main, West Germany.
[5] Ultramid, BASF, Ludwigshafen, West Germany.
[6] Eudragit Retard, Röhm and Haas, Darmstadt, West Germany.

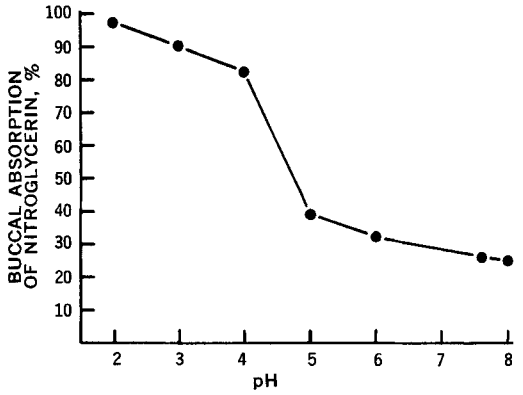

Figure 2—*Buccal absorption of nitroglycerin.*

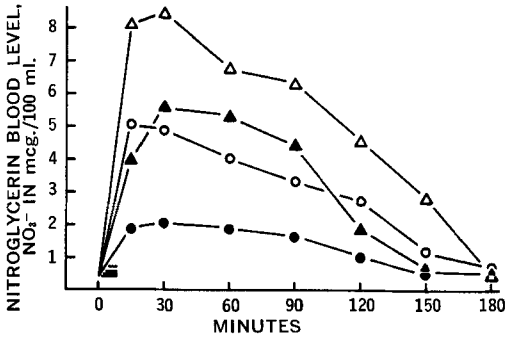

Figure 3—*Numeric plot of nitroglycerin blood levels. Key: △, 1.6 mg. buccally; ▲, 1.6 mg. perorally; ○, 0.8 mg. buccally; and ●, 0.8 mg. perorally.*

Methods—The buccal absorption test was carried out as described by Beckett and Triggs (10), with a slight modification. A buffer solution of the same pH as the test solution was used for rinsing the oral cavity prior to the test and immediately after use of the test solution. The rinsing solution after the test was combined with the expelled test solution.

The spectrophotometric determination of proxyphylline and nitroglycerin (as NO_3^-) in *in vitro* testing and in biological material was described elsewhere (11).

In the present study, the nitroglycerin was first incorporated with the proxyphylline in a matrix tablet by mixing proxyphylline powder of a size $<125\ \mu$ with an alcoholic solution of nitroglycerin. Upon the evaporation of the alcohol, the drug was again passed through a screen of $125\ \mu$. The drug mixture was then mixed with plastic particles between 0.5 and 1 mm. in size, using either polyvinyl chloride or ethylcellulose or the polyamide[5] or polyvinyl acetate, or the polyacrylate[6]. The drug–plastic mixture was then compressed into biconvex tablets of 11-mm. diameter. In *in vitro* evaluation of both proxyphylline and nitroglycerin, a timed release was found from all preparations testing the intact tablets in artificial GI fluid. When the tablets were mechanically divided into two or four parts or powdered, both drugs were released at much faster rates with the increased surface area. As mentioned previously, this problem would not be dangerous with proxyphylline but it would be with nitroglycerin.

To circumvent the fast release of nitroglycerin from accidently masticated or chewed tablets, a technological procedure was sought to act as a safety valve. The following method has been successful. Nitroglycerin, dissolved in an organic solvent [alcohol–acetone (1:1)], was used for impregnation of plastic granules[2] which must be at least partly soluble in the organic solvent employed. After evaporation of the solvent, the plastic–nitroglycerin mass was screened out to particle sizes of 0.5–1 mm. These nitroglycerin–plastic particles were then mixed with proxyphylline and compressed into tablets. For the final preparation, a two-layer tablet was chosen. The first layer, being the initial phase, contained 0.2 mg. of nitroglycerin and 180 mg. of proxyphylline. The drugs were liberated from this initial layer within 5 min. in *in vitro* testing. The depot phase constituted a matrix in which the nitroglycerin (5 mg.) was dissolved in the form of a solid-solid solution in the plastic material[3] and contained 310 mg. proxyphylline (mean particle size $d' = 125\ \mu$) in the pores of the matrix. *In vitro* drug liberation from the timed-release dosage form was determined, using both the half-change method (12) and the modified half-change method (13), adding enzymes (pepsin and pancreatin) in powder form at hourly intervals to the artificial GI fluids.

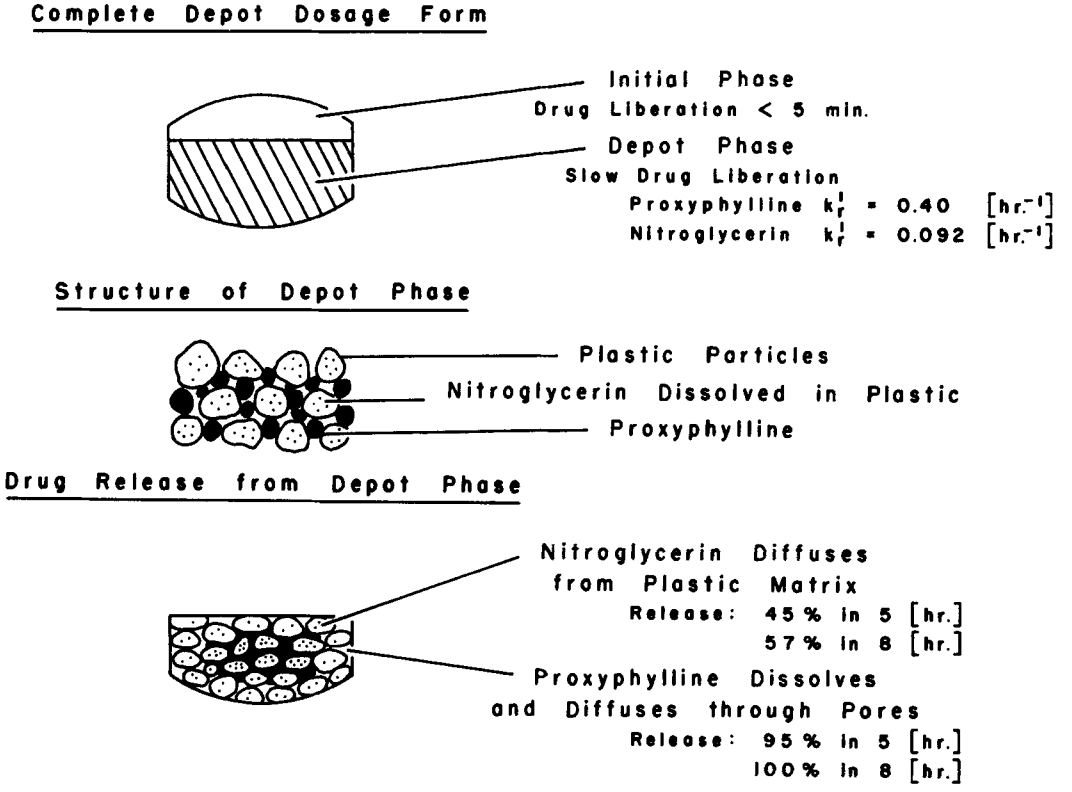

Figure 4—*Diagrammatic structure of the peroral sandwich tablet with timed release and its release characteristics.*

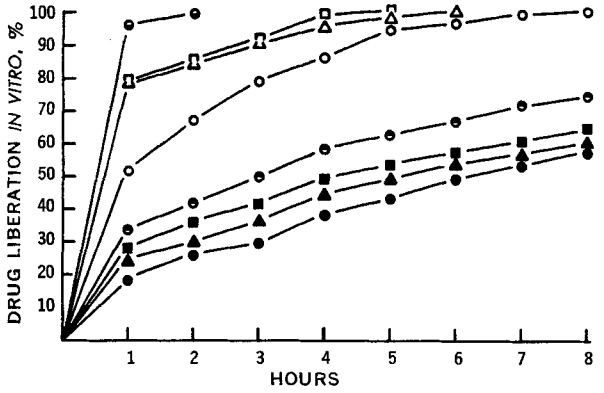

Figure 5—In vitro *drug liberation. Key: Proxyphylline:* ○, *intact tablet;* △, *cut into two parts;* □, *cut into four parts; and* ◒, *powdered. Nitroglycerin:* ●, *intact tablet;* ▲, *cut in.to two parts;* ■, *cut into four parts; and* ◓, *powdered.*

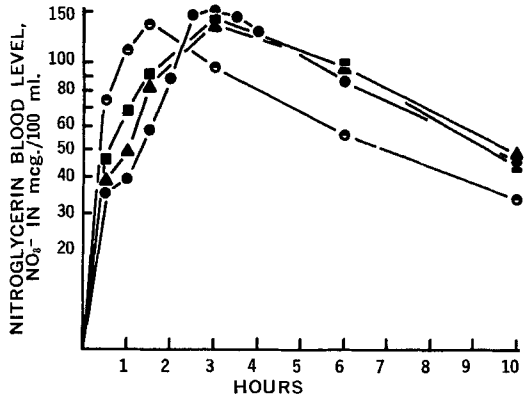

Figure 6—*Nitroglycerin blood level after peroral administration. Key:* ●, *intact tablet;* ▲, *cut into two parts,* ■, *cut into four parts; and* ◓, *powdered and masticated.*

RESULTS AND DISCUSSION

Nitroglycerin Peroral Bioavailability—By using the buccal absorption test, it was found that absorption of nitroglycerin decreased with increasing pH (Fig. 2). From this observation, absorption of nitroglycerin could be anticipated from the acidic stomach.

To study the bioavailability upon peroral administration, nitroglycerin capsules[7] of 0.8 and 1.6 mg. were administered buccally and perorally to three volunteers. The blood levels were determined over 3 hr. and plotted on numeric graph paper under consideration of the blank values (Fig. 3). The areas under the blood level curves (AUC) were determined, and the bioavailability was calculated in percentage according to Eq. 1:

$$\% \text{ bioavailability} = \frac{\text{AUC perorally}}{\text{AUC buccally}} \cdot 100 \qquad \text{(Eq. 1)}$$

For the smaller and higher doses, 35.99 and 54.52%, respectively, were obtained. From this experiment, it was obvious that nitroglycerin is perorally absorbed, although the amount absorbed is less than buccally.

The use of three volunteers allows only a limited evaluation. But if the bioavailability upon peroral administration is only 50%, it is highly questionable whether a potent and toxic drug such as nitroglycerin should be used perorally. Erratic absorption efficiencies could minimize the range between safe and toxic. Furthermore, there seems to be no correlation between hypotensive action of certain aliphatic nitric acid esters and the amount of nitrate and nitrite ions in plasma (14). Onset and action in small doses of organic nitrates is observed to be as rapid as inorganic nitrate, and the clinical effects do not correlate with an elevation of blood nitrate (15). The study described here is, therefore, primarily of academic interest and has to be considered as exemplary of the type of studies that should be conducted for formulating timed-release medications.

***In Vitro* Release Studies**—*In vitro*, the proxyphylline was released from the depot matrix by the apparent first-order rate of $k_r^1 = 0.40\ [h^{-1}]$, and nitroglycerin was released by apparent first-order kinetics of $k_r^1 = 0.092\ [h^{-1}]$. The proxyphylline, incorporated into the pores of the matrix, dissolves as soon as the artificial stomach fluid enters the pores; 95% is released within 5 hr. Nitroglycerin, dissolved in the plastic matrix, must diffuse through the plastic material into the artificial stomach fluid; 45% is released within 5 hr. (Fig. 4).

As was found in a previous clinical study of proxyphylline tablets with timed release (3, 4), the depot effect was lost on mastication. Therefore, drug release was tested *in vitro*. As shown in Fig. 5, the nitroglycerin timed-release pattern was still maintained but the timed release of proxyphylline was certainly lost when tablets were subdivided. Thus, the nitroglycerin should have prolonged activity. This hypothesis was finally verified by *in vivo* experimentation. Figure 6 represents the mean curves from three subjects.

Incorporation of nitroglycerin into plastic granules in the form of a solid-solid solution results in retarded drug release, whereby the main liberation rate-limiting step apparently is the diffusion of nitroglycerin from the plastic granules. The actual surface area is certainly of great influence too but to a lesser extent. *In vivo*, it was found that the actual peak height does not increase upon mastication of the nitroglycerin depot dosage form, but the timed release is markedly reduced. Yet the release is slow enough not to cause unwanted side effects.

The example of nitroglycerin–proxyphylline tablets with timed-release shows that it is possible to incorporate two different drugs with different biological half-lives into one dosage form. Emphasis is given to biopharmaceutical evaluation for drug safety.

[7] Nitrolingual, 0.0008 g., Pohl-Boskamp, Hohenlockstedt, West Germany.

REFERENCES

(1) W. A. Ritschel, *Pharm. Ztg.*, **113,** 1881(1968).
(2) W. A. Ritschel, *Deut. Apoth. Ztg.*, **109,** 236(1969).
(3) W. A. Ritschel and R. Clotten, *Arzneim.-Forsch.*, **19,** 221 (1969).
(4) *Ibid.*, **19,** 347(1969).
(5) W. T. Salter, "A Textbook of Pharmacology," W. B. Saunders, Philadelphia, Pa., 1952, p. 311.
(6) T. Sollmann, "A Manual of Pharmacology," W. B. Saunders, Philadelphia, Pa., 1957, p. 631.
(7) R. A. Turner, *J. Pharm. Sci.*, **54,** 464(1965).
(8) O. J. Lorenzetti, A. Tye, and J. W. Nelson, *ibid.*, **55,** 105 (1966).
(9) M. G. Bogaert, M.-T. Rosseel, and A. F. De Schaepdryver, *Eur. J. Pharmacol.*, **12,** 224(1970).
(10) A. H. Beckett and E.-J. Triggs, *J. Pharm. Pharmacol.*, **19,** 31S(1967).
(11) W. A. Ritschel and R Clotten, *Arzneim.-Forsch.*, **20,** 1180 (1970).
(12) K. Münzel, *Arch. Pharm.*, **293,** 766(1960).
(13) W. A. Ritschel and H. Orth, *J. Pharm. Sci.*, **56,** 773(1967).
(14) J. C. Krantz, C. J. Carr, and S. E. Forman, *J. Pharmacol. Exp. Ther.*, **67,** 191(1939).
(15) L. J. Cass, W. S. Frederik, and H. Dehuca, *Angiology*, **13,** 469(1962).

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