We get the following results for $\partial\beta'/\partial k_{12}$:

$$\frac{\partial\beta'}{\partial k_{12}} < 0 \text{ if } k_{20} < k_{10} + \Delta_1 \quad \text{(Eq. A19a)}$$

$$\frac{\partial\beta'}{\partial k_{12}} = 0 \text{ if } k_{20} = k_{10} + \Delta_1 \quad \text{(Eq. A19b)}$$

$$\frac{\partial\beta'}{\partial k_{12}} > 0 \text{ if } k_{20} > k_{10} + \Delta_1 \quad \text{(Eq. A19c)}$$

where $\Delta_1 = k_{21}[\exp(k_{10}\,\tau) - 1]$.

Note that the test condition does not depend on k_{12} itself. Sensitivity analysis of β' *versus* k_{21} relies on similar algebraic manipulations. Therefore:

$$\frac{\partial\beta'}{\partial k_{21}} < 0 \text{ if } k_{10} < k_{20} + \Delta_2 \quad \text{(Eq. A20a)}$$

$$\frac{\partial\beta'}{\partial k_{21}} = 0 \text{ if } k_{10} = k_{20} + \Delta_2 \quad \text{(Eq. A20b)}$$

$$\frac{\partial\beta'}{\partial k_{21}} > 0 \text{ if } k_{10} > k_{20} + \Delta_2 \quad \text{(Eq. A20c)}$$

where $\Delta_2 = k_{12}[\exp(k_{20}\tau) - 1]$.

Clear-cut results can be given in some cases. If $k_{20} < k_{10}$, $\partial\beta'/\partial k_{12}$ is always negative and if $k_{20} > k_{10}$, the same is true for $\partial\beta'/\partial k_{21}$, regardless of the combination of other parameters. For other cases, the test condition should be computed and applied.

Sensitivity versus *the Elimination Rate Constants* k_{10} *and* k_{20}—Differentiation of f with respect to β' and k_{10} leads to:

$$\frac{\partial\beta'}{\partial k_{10}}[2\beta' - K_1 - K_2 - k_{12}k_{21}\,\tau\exp(\beta'\tau)] = \beta' - K_2 \quad \text{(Eq. A21)}$$

As β' is less than K_2, the second member is negative in the present case. Hence:

$$\frac{\partial\beta'}{\partial k_{10}} > 0 \quad \text{(Eq. A22)}$$

Similarly it can be shown that:

$$\frac{\partial\beta'}{\partial k_{20}} > 0 \quad \text{(Eq. A23)}$$

Therefore, an increase in elimination processes, through either k_{10} or k_{20} will always increase β' and shorten the half-life $T^{\beta'}_{1/2}$.

REFERENCES

(1) L. I. Harrison and M. Gibaldi, *J. Pharm. Sci.*, **65,** 1346 (1976).

(2) H. S. G. Chen and J. F. Gross, *ibid.*, **68,** 792 (1979).

(3) B. E. Dahlström and L. K. Paalzow, *J. Pharmacokinet. Biopharm.*, **6,** 505 (1978).

(4) L. V. Avioli, S. W. Lee, J. E. MacDonald, J. Lund, and H. F. De Luca, *J. Clin. Invest.*, **46,** 983 (1967).

(5) G. Ponchon and H. F. De Luca, *J. Clin. Invest.*, **48,** 1273 (1969).

(6) S. B. Arnaud, R. S. Goldsmith, P. W. Lambert, and V. L. W. Go, *Proc. Soc. Exp. Biol. Med.*, **149,** 570 (1975).

(7) J. D. Lambert, in "The State of the Art in Numerical Analysis," D. Jacobs, Ed., Academic, New York, N.Y., 1977, pp. 451–500.

ACKNOWLEDGMENTS

Presented in part at the "Premier Congrès Européen de Biopharmacie et Pharmacocinétique," Clermont-Ferrand, France, April 1–3, 1981.

Supported in part by a grant from the Caisse Mutuelle Provinciale des Professions Libérales and by funds from the Laboratoire d'Algèbre, Université Paul-Sabatier, F-31000 Toulouse, France.

The authors thank Professor L. Bousquet, Département de Mathématiques, Faculté de Médecine, F-31000 Toulouse Rangueil for computational help at the early stages of the study, Professor S. Guillemant, Laboratoire de Biochimie Médicale, Hôpital de la Pitié, F-75013 Paris for vitamin D_3 data, and the reviewer for helpful comments. The help of Mr. Subra and Mr. Depardieu is also acknowledged.

Combined Water-Soluble Carriers for Coprecipitates of Tolbutamide

M. J. MIRALLES, J. W. McGINTY, and A. MARTIN ˣ

Received January 19, 1981, from the *Drug Dynamics Institute, College of Pharmacy, University of Texas, Austin, TX 78712.* Accepted for publication July 23, 1981.

Abstract □ A study was conducted on the influence of single and combined carriers on the dissolution rate of tolbutamide from its coprecipitates. All of the water-soluble carriers investigated enhanced the dissolution rate of tolbutamide, but the combination of 40% polyethylene glycol 6000–60% dextrose as the carrier for a 1:1 coprecipitate yielded the most rapid dissolution of tolbutamide. Other carriers used were polyethylene glycol 6000, polyethylene glycol 4000, dextrose, and mannitol, alone or combined in various proportions.

Keyphrases □ Tolbutamide—coprecipitates, combined water-soluble carriers, dissolution □ Solubility—combined water-soluble carriers for coprecipitates of tolbutamide, dissolution □ Dissolution—effect of combined water-soluble carriers, coprecipitates of tolbutamide

The rate at which a drug dissolves from its intact or disintegrated and deaggregated form in the GI tract is often responsible for the rate at which the drug appears in the blood, *i.e.*, the absorption rate of the drug. When this is the case, dissolution is said to be the rate-limiting process.

BACKGROUND

The sulfonylurea compounds employed as oral hypoglycemic compounds are considered to be poorly water soluble. Variation in the dissolution rates of these compounds has been reported (1). The influence of *in vitro* dissolution rates on the rate of decline of blood sugar levels has also been studied (2). Varley (3) investigated two formulations of tolbutamide, both generically equivalent in terms of chemical content and USP specifications; he found they were not equivalent as measured by availability of drug to the patient (serum drug levels) or on the basis of therapeutic efficacy (hypoglycemic response). Levy (4) found marked variation in the dissolution rates of two brands of tolbutamide tablets and recommended that patients should not change the brand of the drug they were taking unless the dose of the new brand was established. Another report (5) showed a correlation between percentage of the tolbutamide dose excreted in the urine as its metabolite and the surface area of tolbutamide in the dosage form.

The influence of povidone and polyethylene glycol 6000 on the dissolution rate of tolbutamide was studied (6). It was found that both carriers favorably increased the dissolution rate of the drug and that a complex formed between the drug and povidone but not between tolbutamide and polyethylene glycol. Later it was found (7) that the solid dispersion of

0022-3549/82/0300-0302$01.00/0

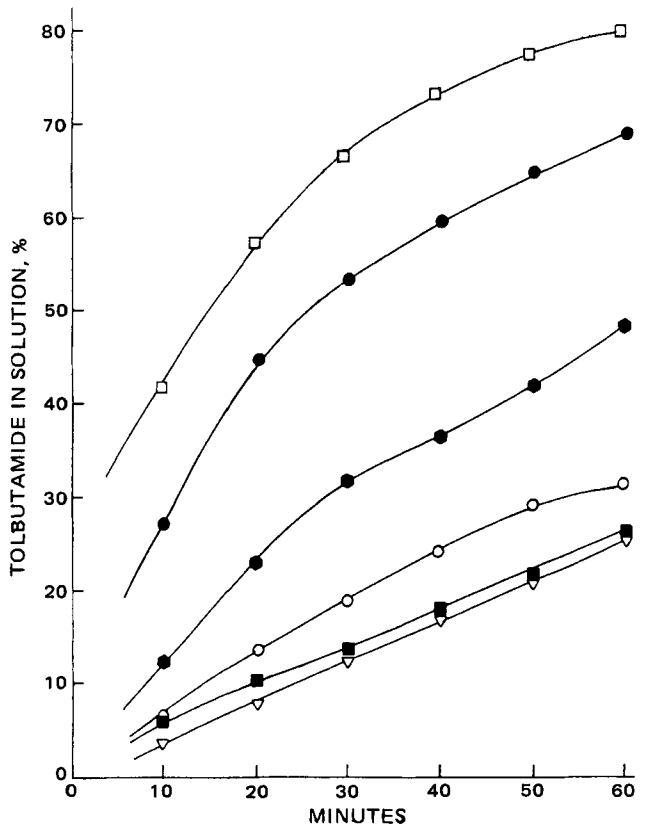

Figure 1—*Dissolution profiles of tolbutamide from its coprecipitates using single carriers. Total amount of tolbutamide: 62.5 mg. Key: ▽, tolbutamide recrystallized from methanol; ■, tolbutamide USP; ○, tolbutamide with mannitol; ●, tolbutamide with dextrose; ●, tolbutamide with polyethylene glycol 6000; and □, tolbutamide with polyethylene glycol 4000.*

tolbutamide in polyethylene glycol and in povidone increased the absorption of the drug and shortened its peak time from 3 hr to <1 hr. Recent reports (8, 9) compared the effect of polyethylene glycol and polyoxyethylene stearate on the dissolution rate and solution properties of tolbutamide from solid dispersions. Sugar combinations have been employed to increase the dissolution rates of hydrocortisone and prednisone (10).

In the present study, the coprecipitation technique was applied to enhance the dissolution rate of tolbutamide. Single and combined water-soluble carriers were utilized and their effects on dissolution rates were compared.

EXPERIMENTAL

Materials—Tolbutamide[1], polyethylene glycol 6000[2], polyethylene glycol 4000[2], dextrose anhydrous[3], and mannitol[3] were obtained commercially.

Preparation of Tolbutamide Coprecipitates—Quantities to make 1:1 coprecipitates of tolbutamide and carrier(s) were weighed accurately and dissolved in a sufficient volume of methanol[4]. The temperature was raised to 37°, and the solvent was allowed to evaporate under the hood, stirring continuously. When evaporation was almost complete, the resulting coprecipitate was removed from the container using a spatula, and placed *in vacuo* for 24 hr. The coprecipitates were sieved and the 100–200 mesh fraction was separated and kept in a desiccator for analysis and dissolution studies. The tolbutamide coprecipitate compositions are shown in Table I.

Dissolution Profiles of Tolbutamide and Tolbutamide Coprecipitates—The dissolution rate studies of tolbutamide and its coprecipitates were done in a dissolution apparatus[5] at 25 ± 0.5°. Nine-hundred

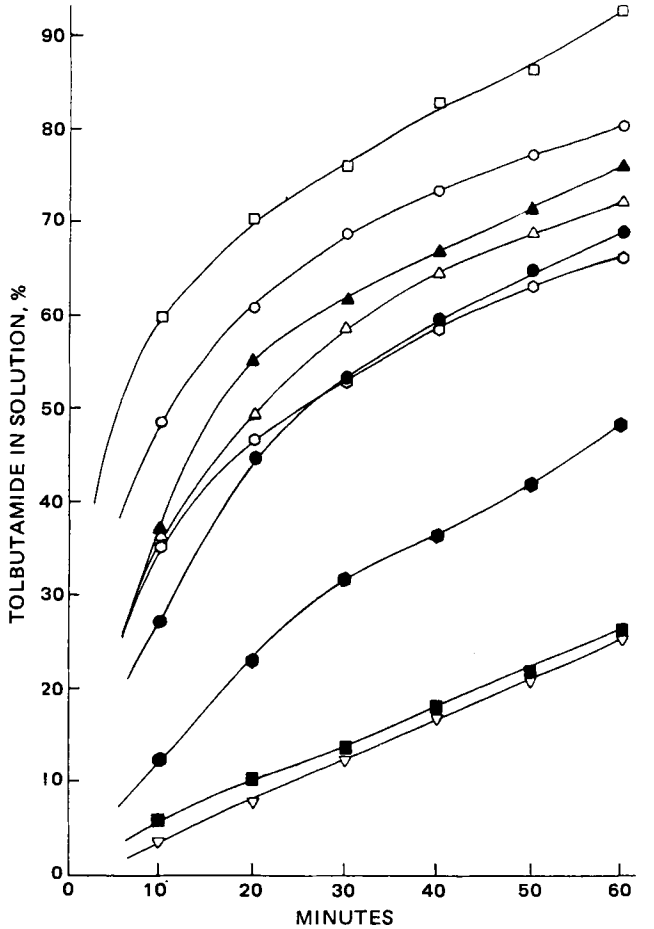

Figure 2—*Dissolution profiles of tolbutamide from its coprecipitates in polyethylene glycol 6000–dextrose carrier systems. Total amount of tolbutamide: 62.5 mg. Key: ▽, tolbutamide recrystallized from methanol; ■, tolbutamide USP; ●, tolbutamide with dextrose; ○, tolbutamide with 20% polyethylene glycol 6000–80% dextrose; ●, tolbutamide with polyethylene glycol 6000; △, tolbutamide with 60% polyethylene glycol 6000–40% dextrose; ▲, tolbutamide with 70% polyethylene glycol 6000–30% dextrose; ○, tolbutamide with 80% polyethylene glycol 6000–20% dextrose; and □, tolbutamide with 40% polyethylene glycol 6000–60% dextrose.*

milliliters of deionized water was placed in the vessels, the paddle stirring speed was set at 150 rpm, and 125 mg of the coprecipitate or 62.5 mg of the drug were added to the medium after the temperature was reached. The paddle was placed 2.5 cm from the bottom of the vessel. A glass filter[6] was attached to a 3-way stopcock[7] and this was attached to a glass syringe. One milliliter of filtrate was removed every 10 min and diluted to 10 ml with deionized water. The volume in the vessel was replaced with deionized water after each sample was taken. The absorbances of the solutions were measured in a spectrophotometer[8] at 230 nm using deionized water as the blank. None of the carriers interfered with the measurement of the absorbances at this wavelength.

RESULTS AND DISCUSSION

Tolbutamide Content of the Coprecipitates—The tolbutamide coprecipitates were assayed by spectrophotometry at λ_{max} = 230 nm using a 5% (v/v) dilution of methanol in deionized water as the blank. The drug content of the tolbutamide coprecipitates was within the 48.9–51.9% (w/w) range.

Dissolution Profiles of Tolbutamide Alone and from Its Coprecipitates—The dissolution profiles of tolbutamide alone, (100/200 mesh, and tolbutamide recrystallized from methanol and sieved to a 100/200 mesh) and with tolbutamide coprecipitates containing single carriers,

[1] The Upjohn Co., Kalamazoo, Mich.
[2] Union Carbide Corp., New York, N.Y.
[3] Matheson Coleman and Bell Manufacturing Chemists, Norwood, Ohio.
[4] Fisher Scientific Co., Fair Lawn, N.J.
[5] Easi-Lift model 72SL dissolution apparatus, Hanson Research Corp., Northridge, Calif.
[6] Kimble model 28630 gas dispersion tube, size 12-C, Owens-Illinois, Toledo, Ohio.
[7] K-75 three-way stopcock, Pharmaseal Inc., Toa Alta, Puerto Rico.
[8] Beckman model 25 spectrophotometer, Beckman Instruments Inc., Fullerton, Calif.

Table I—Composition of 1:1 Tolbutamide Coprecipitates

Polyethylene Glycol 6000, %	Dextrose, %
100	0
80	20
70	30
60	40
40	60
20	80
0	100
Polyethylene glycol 4000, %	**Mannitol, %**
100	0
80	20
60	40
50	50
40	60
20	80
0	100

are shown in Fig. 1. The dissolution profiles of tolbutamide from the two combination carrier systems (polyethylene glycol 6000–dextrose and polyethylene glycol 4000–mannitol) are shown in Figs. 2 and 3, respectively. Each point in these plots corresponds to the average of six determinations. The dissolution studies of tolbutamide from its coprecipitates showed that the presence of the water-soluble carrier enhanced the dissolution rate of the drug in all cases as compared with plain and recrystallized tolbutamide. From Fig. 1 it can be seen that the increase in the dissolution rate of tolbutamide was more pronounced when polyethylene glycol 4000 was used as the carrier than when polyethylene glycol 6000 was the drug vehicle. Dextrose alone and mannitol alone produced little increase in dissolution rate, but the combination of these carriers with polyethylene glycol 6000 and polyethylene glycol 4000 produced a large increase in dissolution rate of the drug in all proportions studied. The combination of 40% polyethylene glycol 6000–60% dextrose produced the highest dissolution rate of tolbutamide from its coprecipitates. If single carriers were desired, polyethylene glycol 4000 would be the carrier of choice with 44% of drug released after 10 min of the dissolution test. When carrier combinations were studied, ~60% of the drug was dissolved after 10 min for a coprecipitate of the drug in 40% polyethylene glycol 6000–60% dextrose. Approximately the same results were obtained when 50% polyethylene glycol 4000–50% mannitol was employed. It can be seen from Figs. 1–3 that the amount of the drug dissolved increased more than 15 times during the first 10 min of the dissolution study as compared with the dissolution of recrystallized tolbutamide; it was ~3 times higher after 1 hr when the drug was dispersed in a 40% polyethylene glycol 6000–60% dextrose mixture. When mannitol was the carrier, the amount dissolved increased only ~1.5 times indicating that mannitol, in the ratio of drug to carrier investigated (1:1), was a poor carrier for tolbutamide. Polyethylene glycol 6000 has been extensively used as a water-soluble carrier for slightly soluble drugs and has been claimed as a universal carrier. However, in this case the amount of drug dissolved increased only ~5 times as compared with the dissolution of recrystallized tolbutamide.

It is important to point out that only the 1:1 coprecipitates were investigated and that the enhancement of dissolution rates of tolbutamide from its coprecipitates would be expected to increase when the ratio of drug to carrier is diminished.

CONCLUSIONS

The 100–200 mesh fraction of the 1:1 coprecipitates of tolbutamide with dextrose, mannitol, polyethylene glycol 6000, polyethylene glycol 4000, and combinations of polyethylene glycol 6000–dextrose and polyethylene glycol 4000–mannitol in different proportions showed a faster dissolution *in vivo* than plain tolbutamide or tolbutamide recrystallized from methanol.

The use of combined carriers in the preparation of the coprecipitates of tolbutamide constituted an advantage over the formulation of the solid dispersions in a single carrier. The carrier combination consisting of 40% polyethylene glycol 6000–60% dextrose provided the fastest dissolution of the drug from its coprecipitate. Since polyethylene glycol 4000 alone produced a faster dissolution of tolbutamide than polyethylene glycol 6000 alone, and dextrose alone gave a faster dissolution of the drug than did mannitol alone, it is probable that combinations of polyethylene glycol 4000–dextrose would result in a better carrier system for tolbutamide. Further investigation is needed to support this suggestion.

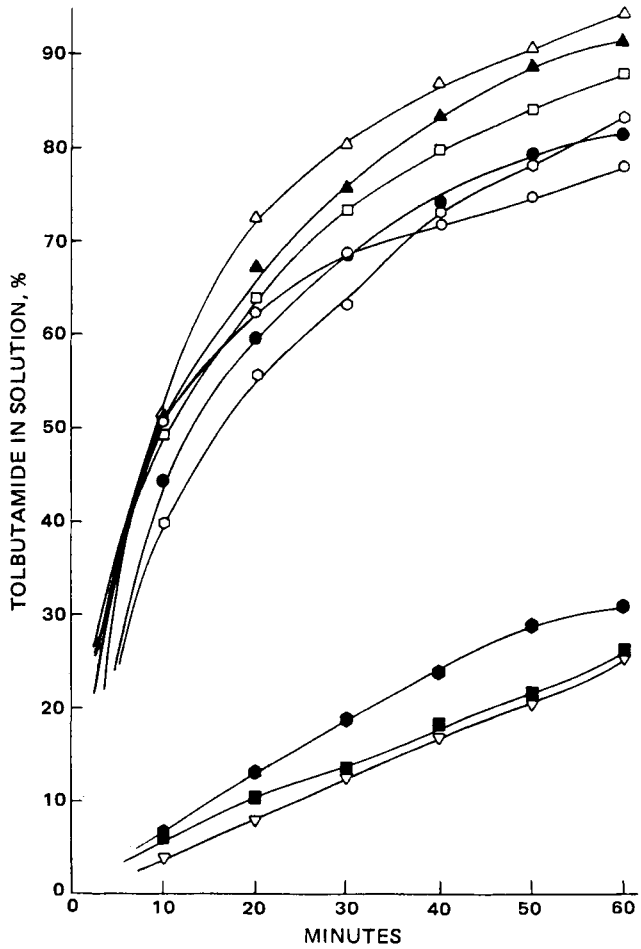

Figure 3—*Dissolution profiles of tolbutamide from its coprecipitates in polyethylene glycol 4000–mannitol carrier systems. Total amount of tolbutamide: 62.5 mg. Key: ▽, tolbutamide recrystallized from methanol; ■, tolbutamide USP; ●, tolbutamide with mannitol; ○, tolbutamide with 20% polyethylene glycol 4000–80% mannitol; ●, tolbutamide with polyethylene glycol 4000; ○, tolbutamide with 80% polyethylene glycol 4000–20% mannitol; □, tolbutamide with 40% polyethylene glycol 4000–60% mannitol; ▲, tolbutamide with 60% polyethylene glycol 4000–40% mannitol; △, tolbutamide with 50% polyethylene glycol 4000–50% mannitol.*

REFERENCES

(1) J. F. Nash, J. A. Galloway, A. D. Garner, D. W. Johnson, I. W. Kleber, and B. A. Rodda, *Can. J. Pharm. Sci.*, **12**, 59 (1977).

(2) E. Nelson, E. L. Knoechel, W. E. Hamlin, and J. G. Wagner, *J. Pharm. Sci.*, **51**, 509 (1962).

(3) A. B. Varley, *J. Am. Med. Assoc.*, **206**, 1745 (1968).

(4) G. Levy, *J. Can. Med. Assoc.*, **90**, 978 (1964).

(5) E. Nelson, S. Long, and J. G. Wagner, *J. Pharm. Sci.*, **53**, 1224 (1964).

(6) S. A. Said, H. M. El-Fatatry, and A. S. Geneidi, *Aust. J. Pharm. Sci.*, **NS3**, 42 (1974).

(7) S. A. Said and S. F. Saad, *ibid.*, **NS4**, 121 (1975).

(8) R. Kaur, D. J. W. Grant, and T. Eaves, *J. Pharm. Sci.*, **69**, 1317 (1980).

(9) *Ibid.*, **69**, 1321 (1980).

(10) L. V. Allen, Jr., R. S. Levinson, and D. Martono, *J. Pharm. Sci.*, **67**, 979 (1978).

ACKNOWLEDGMENTS

This work was supported in part by an endowed professorship provided to A. Martin by Coulter R. Sublett.

M. J. Miralles expresses her gratitude to the Venezuelan government for providing her with continuous financial support over the time this investigation was conducted.