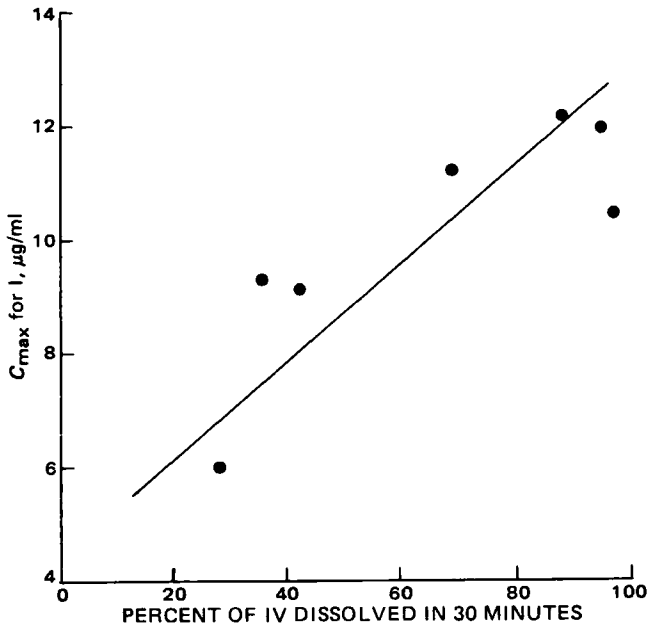

Figure 1—*Relationship between the* in vivo *measure of* C_{max} *for I and the* in vitro *measure of percent IV dissolved in 30 min for the seven trisulfapyrimidine suspensions, showing the regression line for the correlation coefficient of +0.83 (*$p < 0.05$*).*

observed in the rate and extent of absorption of individual suspension components. An *in vitro* dissolution test procedure was developed and dissolution samples analyzed by HPLC. Several significant correlations were reported between *in vivo* and *in vitro* parameters for individual sulfa components. Results of the present investigation show that when using the same dissolution procedure but a different method of detection (UV spectrophotometric) statistically significant correlations could be achieved between the *in vitro* values of percent of total sulfa drug dissolved (in 15 and 30 min) and the *in vivo* parameters reported previously for I and II.

As reported previously, the greatest bioavailability difference among the seven products was observed for the C_{max} parameter for I, for which good correlation was shown with the percent of I dissolved in 30 min (as measured by HPLC). The results of this study also show good correlation ($r = 0.83$, $p < 0.05$) between C_{max} for I and percent of IV dissolved in 30 min, as shown in Fig. 1. Thus, the UV method can be employed for studying the dissolution of trisulfapyrimidine suspensions. The method offers certain advantages over the HPLC procedure in that it is more rapid, less expensive, readily available in most laboratories, and more easily applicable to automation technology. Except for the fact that it could not detect differences in the individual sulfa components of trisulfapyrimidines, the UV method was found to be suitable for the determination of dissolution properties of commercial products.

ACKNOWLEDGMENTS

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REFERENCES

(1) Y. Langlois, M. A. Gagnon, and L. Tetreault, *J. Clin. Pharmacol.*, **12**, 196 (1972).

(2) V. Bernareggi, G. Bugada, A. Cassola, G. Levi, and F. Moncalvo, *Boll. Chim. Farm.*, **112**, 177 (1973).

(3) S. A. Khalil, M. A. Moustafa, A. R. Ebian, and M. M. Motawi, *J. Pharm. Sci.*, **61**, 1615 (1972).

(4) M. J. Taraszka and R. A. Delor, *J. Pharm. Sci.*, **58**, 207 (1969).

(5) G. R. VanPetten, G. C. Becking, R. J. Withey, and H. F. Lettau, *J. Clin. Pharmacol.*, **11**, 27 (1971).

(6) G. R. VanPetten, G. C. Becking, R. J. Withey, and H. F. Lettau, *J. Clin. Pharmacol.*, **11**, 35 (1971).

(7) R. J. Withey, G. R. VanPetten, and H. F. Lettau, *J. Clin. Pharmacol.*, **12**, 190 (1972).

(8) G. L. Mattok and I. J. McGilveray, *J. Pharm. Sci.*, **61**, 746 (1972).

(9) L. Mathur, J. M. Jaffe, R. I. Poust, H. Barry, III, T. J. Goehl, V. P. Shah, and J. L. Colaizzi, *J. Pharm. Sci.*, **68**, 699 (1979).

(10) T. J. Goehl, L. Mathur, J. D. Strum, J. M. Jaffe, W. H. Pitlick, V. P. Shah, R. I. Poust, and J. L. Colaizzi, *J. Pharm. Sci.*, **67**, 404 (1978).

(11) "The United States Pharmacopeia," 20th rev., U.S. Pharmacopeial Convention, Rockville, Md., 1980, p. 959.

Quantitative Assessment of the Effect of Some Excipients on Nitrazepam Stability in Binary Powder Mixtures

P. R. PERRIER and U. W. KESSELRING ˣ

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Abstract □ The decomposition rate constants, normalized for dilution and relative specific surface effects, of nitrazepam in simple binary powder mixtures with talcum, lactose·H_2O, microcrystalline cellulose, corn starch, mannitol, and saccharose are shown to be linearly related to the nitrogen adsorption energy of the excipients.

Keyphrases □ Nitrazepam—effect of excipients on stability in binary powder mixtures □ Excipients—effect on nitrazepam stability in binary powder mixtures

Recently, considerable effort has been made to precisely describe the chemical properties of excipients and how these excipients influence the technical and biopharmaceutical characteristics of the dosage forms. Excellent reviews list the "inert compounds" of pharmaceutical preparations (1), describe the difficulties concerning the "choice of excipients for international use" (2), "the influence of excipients on the design and manufacture of tablets and capsules" (3), and the "problems of drug interactions with excipients" (4). Many studies describe the influence of excipients, *e.g.* the acid-catalyzed decomposition of digoxin by montmorillonite (5), the effect of water adsorption properties of silica gel on the stability and the biological availability of ascorbic acid (6), and the influence of the solubility of some excipients on *in vitro* and *in vivo* properties of bendroflumethiazide tablets (7). Additional references were cited by Carstensen (8, 9).

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Table I—Sample Description, Nitrogen Adsorption Energies and Decomposition Rate Constants [a]

Excipient	Density, g/cm³	Specific Surface (Σ), m²/g	$\frac{\Sigma_I}{\Sigma_e}$	Dilution Factor[b], $\frac{C_e}{C_I} = \frac{100 - C_I}{C_I}$	10^3k, day⁻¹	$10^3k_{0.5}\frac{\Sigma_I}{\Sigma_e}$, day⁻¹	E_{ads} (N_2), kcal/g
Talcum	2.841	2.53	0.451	199.3	6.11	2.77	2.04
Lactose·H_2O	1.545	2.15	0.530	204.5	8.86	4.59	2.00
Microcrystalline cellulose	1.530	1.39	0.820	105.8	5.04	7.81	1.90
Corn starch	1.504	0.55	2.073	199.2	5.31	11.1	1.87
Mannitol	1.486	0.45	2.533	200.8	5.67	14.3	1.78
Saccharose	1.587	0.28	4.071	199.4	4.44	18.1	1.74
Nitrazepam	1.398	1.14					

[a] These data were normalized to 0.5% dilution, and corrected for surface effect, (Σ_I/Σ_e), of nitrazepam, I, mixed with various excipients, e, stored at 70° and 60% relative humidity. [b] Expressed in terms of C_I, mg of nitrazepam, and C_e, mg of excipient per 100 mg of sample.

BACKGROUND

No systematic approach has been made to quantitatively study the so-called "inertness" of excipients. The work reported here is a first attempt to assess quantitatively (under well-defined conditions) the influence of some commonly used excipients on nitrazepam stability to find some parameter(s) which permit an objective comparison of the inertness of excipients.

Assuming a pseudo-first-order degradation, it has been shown that the logarithm of the nitrazepam decomposition rate constant is proportionally related to the inverse of absolute temperature and to the relative humidity of the environment (10). Other parameters to be considered are the dilution of the active ingredients and the relative specific surface area of the components of the system.

It is assumed that the slight concentration differences in the individual samples used in this study (<5%, except for the cellulose system, where the nitrazepam concentration was 1%, as compared with 0.5% in the other samples) may be linearly normalized[1].

These parameters must all be known and taken into account for further discussion and eventual elucidation of their influence on reaction mechanism. Because direct chemical reaction with the so-called "inert" excipients can be excluded in most cases, the hypothesis is formulated that the solid-state nitrazepam decomposition might be treated in analogy to heterogeneous catalysis reactions (11) whose basic steps are:

1. diffusion of the reactant toward the catalyst;
2. adsorption of the reactant onto the catalyst;
3. reaction of the adsorption complex to yield the product;
4. desorption of the product from the catalyst;
5. diffusion of the product away from the catalyst.

Anyone of these steps can be rate controlling for a given process, but not all the steps are necessarily involved in all decomposition reactions encountered in solid-state pharmaceutical dosage forms.

Before elucidating reaction mechanisms it would seem reasonable to study the role of water and to find out whether the reacting water molecules are in the gaseous, liquid, or some intermediate state, and whether it is possible to define a quantity of "water available for reaction" according to the following equation:

$$A_{sol} + (H_2O)_n \cdot B \rightarrow C_{sol} + D_{sol} + B \cdot (H_2O)_{n-1}$$

The difficulty of evaluating hygroscopicity for pharmaceutical solids has recently been described by van Campen *et al.* (12).

Also, the adsorption properties of the aerosol play an important role in nitrazepam stability (13).

EXPERIMENTAL

Materials—Nitrazepam (1,3-dihydro-7-nitro-phenyl-2*H*-1,4-benzodiazepin-2-one)[2], microcrystalline cellulose[3], talcum[4], mannitol[4], lactose·H_2O[4], cornstarch[4], and saccharose[4] were supplied commercially. Microcrystalline cellulose was used as received, all other excipients were of Pharmacopoea Helvetica VI quality. Adsorption isotherms and specific surfaces were determined with nitrogen (purity: 99.998%)[5].

Sample Preparation and Storage Conditions—Individual 800-mg samples containing 4 mg (0.5%) of nitrazepam were prepared by carefully mixing the constituents and avoiding any alteration of the granulometric characteristics. The samples were stored in climatic chambers[6] at constant relative humidity (60 ± 2%) and temperature (70 ± 0.5°).

Density and Specific Surface Area Determinations—True density values were obtained by means of a commercial pycnometer[7] measuring the helium gas or air volume displacement by the dried sample with a precision of 0.02 ml for a total volume of 15 ml. The specific surface area and the nitrogen energy of adsorption on the excipients were obtained by means of a homemade manifold, calculated according to the BET theory (14). The precision of the surface values obtained by nitrogen adsorption at 77°K is 1% for surfaces smaller than 1 m^2g^{-1} and better than 1% for surfaces larger than 1 m^2g^{-1}.

Assay—The decomposition of nitrazepam has been followed by HPLC using a liquid chromatograph[8] with a dualwave UV detector linked to an electronic integrating recorder[9] and fitted with a silica-filled column

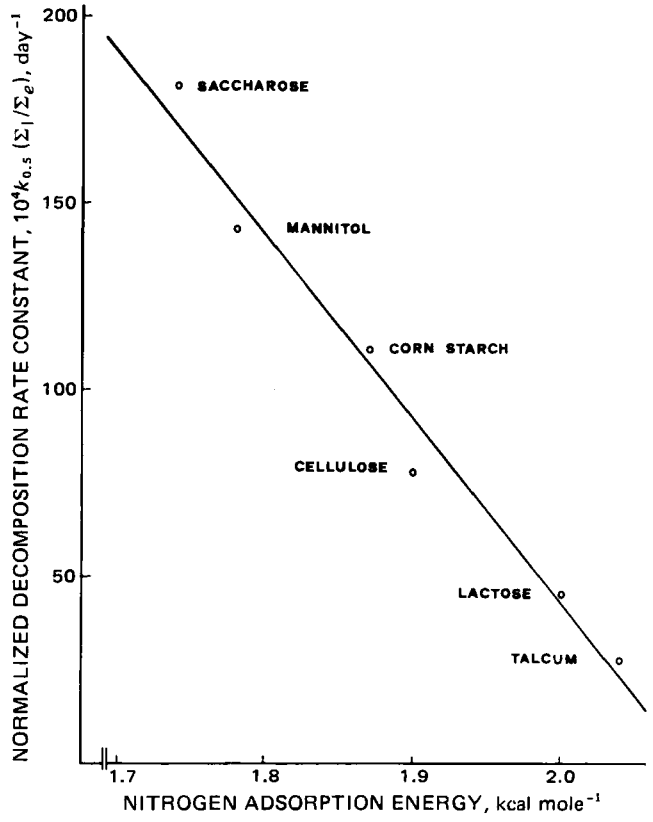

Figure 1—*Normalized decomposition rate constants of nitrazepam in relation to the nitrogen adsorption energy of various excipients.*

[1] Unpublished results from this laboratory; manuscript in preparation.
[2] F. Hoffmann-La Roche and Co. S.A., CH-4000 Basel, Switzerland.
[3] Avicel PH 101, Interchemie A.G., CH-8001 Zürich, Switzerland.
[4] Siegfried A.G., CH-4800 Zofingen, Switzerland.
[5] $N_2$48, Air Liquide Co., CH-1211 Genève, Switzerland.
[6] Voetsch VTKTR and VTKTR 125S, Heraeus-Laborgeräte S.A., CH-1227 Carouge-Genève, Switzerland.
[7] Air Comparison Pycnometer model 930, Instrumenten Gesellschaft A.G., CH-1227 Carouge-Genève, Switzerland.
[8] Liquid Chromatograph Spectra-Physics model 3500, Spectra-Physics A.G., CH-4054 Basel, Switzerland.
[9] Minigrator, Spectra-Physics A.G., CH-4054 Basel, Switzerland.

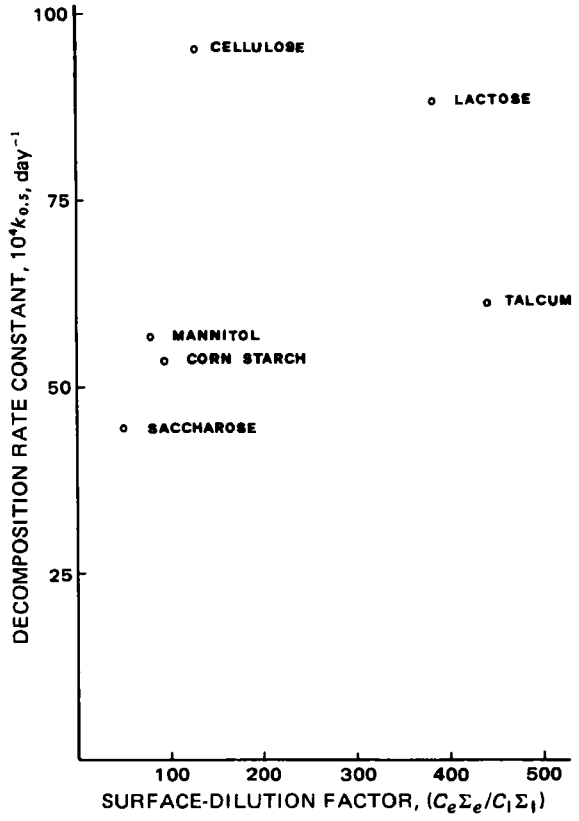

Figure 2—*Decomposition rate constants of nitrazepam as a function of the surface-dilution factor.*

(0.3 × 25 cm)[10]. To maintain column efficiency a precolumn of 0.3 × 5 cm, with identical filling, served as the filter. Operating conditions were as follows: mobile phase composition was *n*-hexane–chloroform–methanol (83.25:12.5:2.25), flow rate was 1.8 ml/min at a pressure of ~79 atm.

Antipyrine (2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) at a concentration of 1.063×10^{-3} moles/liter served as the internal standard. The linearity range of nitrazepam was from 0.04 to 4 μg. Recovery of nitrazepam at 0.5% in microcrystalline cellulose was >98%, and the precision obtained was better than 1% for assays of amounts of I >0.04 μg and better than 2% for quantities <0.04 μg.

RESULTS AND DISCUSSION

Based on the experimental results obtained (Table I) the following linear relationship was established:

$$10^3 k_{0.5} \frac{\sum_I}{\sum_e} = 102 - 49.0\, E_{ads}(N_2) (r^2 = 0.976 \text{ for } n = 6)$$

where $k_{0.5}$ is the decomposition rate constant for a sample containing exactly 0.500% nitrazepam, Σ is the specific surface (m^2g^{-1}), (I is nitrazepam and *e* is the excipient), and $E_{ads}(N_2)$ is the nitrogen adsorption energies in which the nitrazepam decomposition constant decreases proportionally to the increase of nitrogen adsorption energy on the six excipients (Fig. 1).

If the contact surface were the only influence an excipient had, and assuming similar excipient surface coverage by the drug, then all decomposition rate constants of nitrazepam, once corrected for dilution and relative specific surface areas of the sample components, should be identical, whatever excipients are used. As can be seen in Fig. 2, this is not the case; each excipient has its own specific and/or nonspecific influence on the observed rate. In the case of hydrolytic decomposition and according to the law of mass action, the amount of water present as a reagent (as long as not in excess) has a direct influence on the reaction rate. At present there is no possibility of determining quantitatively and directly the amount of water available and usable for reaction in a solid-state sample and the exact physical state of the reacting water. There is, however, no doubt that both the physical and the structural states of the water are strongly influenced by adsorption properties of the excipients. In the case of nitrazepam decomposition, the reaction rate diminishes with increasing nitrogen adsorption energy of the excipients.

From structural considerations, there is no reason to expect that the nitrazepam adsorption energy would be affected by the various excipients used. Since the only other reactant is water, a hypothetical conclusion can be drawn that the availability, *i.e.* reactivity, of water is the important parameter in the experimental system considered and that the water-binding energy to the excipients is the important factor to look at. Since only adsorbed water molecules may react, and their reactivity is inversely related to their adsorption energy, it is necessary either to establish the relationship between E_{ads} (N_2) and E_{ads} (H_2O), the adsorption energy of (for the reaction available) water, and/or to determine the relative water binding forces to the excipient.

[10] Spherisorb Silica 5 μm, SS-3-250-S5W, Spectra-Physics A.G., CH-4054 Basel, Switzerland.

REFERENCES

(1) J. Cooper, *Drug Dev. Ind. Pharm.*, **5**, 293 (1979).

(2) H. Hess, *Drug Dev. Ind. Pharm.*, **3**, 491 (1977).

(3) T. M. Jones, *Drug Cosmet. Ind.*, **(1979)** 40.

(4) P. H. Stahl, "Proceedings of the 39th International Congress of Pharmaceutical Science," (FIP, Brighton, Sept. 3–7, 1979), Elsevier, North-Holland Biomedical Press, 1980, pp. 265–280.

(5) L. S. Porubcan, S. Born, J. L. White, and S. L. Hem, *J. Pharm. Sci.*, **68**, 358 (1979).

(6) E. de Ritter, L. Magid, M. Osadca, and S. Rubin, *J. Pharm. Sci.*, **59**, 229 (1970).

(7) M. H. Rubinstein and M. Birch, *Drug Dev. Ind. Pharm.*, **3**, 439 (1977).

(8) J. T. Carstensen, "Pharmaceutics of Solids and Solid Dosage Forms," Wiley, New York, N.Y., 1977, pp. 182–206.

(9) J. T. Carstensen, "Solid Pharmaceutics: Mechanical Properties and Rate Phenomena," Academic, New York, N.Y., 1980, pp. 237–245.

(10) D. Genton and U. W. Kesselring, *J. Pharm. Sci.*, **66**, 676 (1977).

(11) J. Fripiat, J. Chaussidon, and A. Jelli, "Chimie Physique des Phénomènes de Surface," Masson, Paris, 1971, pp. 201–227.

(12) L. van Campen, G. Zografi, and J. T. Carstensen, *Int. J. Pharm.*, **5**, 1 (1980).

(13) J. Czaja and J. B. Mielck, *Pharm. Acta Helv.*, **57**, 144 (1982).

(14) S. Brunauer, P. H. Emmet, and E. Teller, *J. Am. Chem. Soc.*, **60**, 309 (1938).

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