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Sustained release delivery systems. III. Preparation and in vitro dissolution of surface-reacted dapsone particles

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Summary

The use of low solubility materials as coating agents to prepare sustained release particles is well known. Distinct from this physical process, the present work was undertaken to assess the feasibility of chemically forming a low solubility derivative, or derivatives, on the surface of a drug particle. Accordingly, the surface reaction of solid dapsone (DDS) particles exposed to acetic anhydride vapor was studied as a function of time, temperature, particle size, and particle type (compressed and precipitated). The in vitro dissolution of these particles was also studied. Over time, DDS was converted to monacetyldapsone (MADDS) and diacetyldapsone (DADDS). The temperature-controlled reaction studies were carried out using a small rotating basket that contained the DDS powder while being permeable to acetic anhydride vapor. The extent of conversion as a function of time was determined by removing samples at known time intervals and assaying for DDS, MADDS and DADDS using HPLC. At any one time, the fraction of DDS acetylated decreased with increasing particle size. The time course of the reaction for compressed particles was different from that for precipitated particles. Temperature studies suggested that the conversion reaction of the precipitated particles was under chemical control while that for compressed particles was under diffusion control. In either case, it appeared that conversion proceeded in accordance with the so-called "shrinking unreacted core" model, which resulted in the formation of an external layer of MADDS and DADDS that increased in thickness with time, while the diameter of the unreacted core decreased. That such a low solubility layer had an influence on the release of the unreacted drug core was confirmed by in vitro dissolution studies. As the content of DADDS in the reacted layers increased, the rate of dissolution of DDS from the core decreased markedly.

Introduction

The development of novel delivery systems designed to be site-specific and/or achieve controlled release has been actively pursued in recent years. Drug delivery has been controlled using fabricated devices or techniques such as encapsulation, complexation, and coating. Liposomes, nanoparticles and microspheres are under investigation, as are biodegradable and non-biodegradable polymers intended to entrap or coat the drug. The physical principles upon which many of these systems and formulations depend have been well reviewed (Robinson, 1978; Juliano, 1980; Chien, 1982; Deasy, 1984). Chemical approaches have been developed to achieve both site-specific and controlled release (Roche, 1977; Sinkula, 1978;

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Stella et al., 1980). Controlled delivery dosage forms offer several potential advantages over conventional dosage forms. These include reduced frequency of dosing, effective use of drugs with short half-lives, improved patient compliance, and reduction of side-effects and toxicity. Their use in chronic disease states is particularly attractive, since it is believed that patient compliance drops as chronic therapy continues. Anti-hypertensive, anti-inflammatory, anti-asthmatic, anti-psychotic, anti-malarial, anti-coagulant and anti-leprotic therapy could all benefit from the use of delivery systems administered regularly but less frequently.

Leprosy is a chronic communicable disease that is estimated to afflict 12 million people. The causative organism is *Mycobacterium leprae*. A drug widely used in the treatment of leprosy is dapsone (DDS, 4,4′-diaminodiphenylsulfone). Work by Glazko et al. (1968), Ellard (1975), Shepard et al. (1976) and Lammintausta et al. (1979) indicates that the drug, following oral administration, is slowly but completely absorbed. A variety of oral dosage regimens have been used; 50–100 mg daily or every other day appears to be the one most frequently used once the patient has been on the drug for 3–4 months. Depending on the type of leprosy, drug therapy may be continued for 5 years or longer. While DDS is effective and relatively inexpensive, resistant strains of *M. leprae* have developed due to the use of inadequate doses of the drug and/or poor patient compliance during the long-term therapy associated with this disease. These factors have created interest in the development of an intra-muscular sustained release formulation containing 1200–1500 mg DDS as a 30% suspension that would be administered no more frequently than once a month.

With the notable exception of acedapsone (DADDS), there has been little successful development of sustained release formulations of dapsone. Glazko et al. (1968) showed that a 300 mg intramuscular dose of DADDS produced a peak plasma level of about 0.06 μg/ml in 6 days followed by plateau levels of 0.030–0.035 μg/ml. These levels then lasted for 60 days. Elslager (1974) believed acedapsone to be effective as an anti-leprotic at an intramuscular dose of 225 mg every 77 days. While such a regimen should improve patient compliance, the levels of DDS resulting from in vivo dissolution of DADDS, and its subsequent hydrolysis to DDS and MADDS are now considered to be only marginally effective therapeutically.

Modderman et al. (1982) in a preliminary study in man, prolonged the duration of action of DDS to approximately 3 weeks by administering 1200 mg intramuscularly, with 80% of the particles 90–125 μm and the remainder below this range. The effect of size on the in vitro dissolution rate of DDS particles was shown to be predictable by Swarbrick and Ma (1981), with dissolution being related to the reciprocal of the geometric mean diameter. However, there are limits to the extent to which particle size can be increased in order to slow dissolution and release in vivo. These are due to the poor syringeability of dispersions containing large particles and the maximum needle size tolerated by the patient on injection. Thus 125–150 μm appears to represent the largest particle suspension that can be conveniently injected.

Swarbrick (1984) has recently described an approach for the preparation of controlled release solid particles using a novel technique in which a less soluble derivative, or derivatives, is formed in situ as a coat or layer around the original material. This coat must partially dissolve and/or disrupt before the core material is released. This "surface reaction" approach is feasible with DDS, since its acetylated derivatives (monacetyldapsone, MADDS and diacetyldapsone, DADDS) are approximately 10 and 50 times, respectively, less soluble than DDS. In man, DADDS is irreversibly deacetylated to MADDS and DDS and all three compounds are present in circulating plasma. However, DDS and MADDS are in dynamic flux, with acetylation and deacetylation occuring concurrently. Following the administration of DDS or MADDS, no acetylation to form DADDS occurs (Murray et al., 1971; Peters et al., 1977). Since in man DADDS and MADDS are capable of conversion to DDS, the materials used to control release also contribute to the pharmacological effect since they revert to the active agent. As such, they are also biodegradable.

This paper, one of a series of studies exploring

approaches to slow dissolution and extend therapeutic effect (Yang and Swarbrick, 1986 a and b), describes work conducted to elucidate and quantitate the surface reaction of DDS particles and the effect on in vitro dissolution. The chemical conversion of solid particles by reaction with a gas is a complex phenomenon, involving not only the shape, porosity and size of the particles, but the nature and physical state of the reactants and products. The overall rate may be controlled by the rate at which the chemical reaction occurs at an interface, the rate of diffusion of reactant(s) to this interface, or both (Szekely et al., 1976). If one or more of the products is gaseous, the overall size of the particle will decrease as the reaction proceeds. In the present study, the chemical products of the reaction (MADDS and DADDS) are solids of approximately equal density to DDS; hence, no net change in particle size should occur on reaction.

In general, with non-porous solid particles reacting to form solid product(s), the reaction occurs in a narrow region or interface between the unreacted core and the product layer (Fig. 1a). This is referred to as the "shrinking unreacted core" model, and occurs irrespective of whether the reaction is under chemical or product layer diffusion control. The product(s) may or may not be porous; in the latter case, a chemically-controlled reaction may become diffusion-controlled as conversion proceeds.

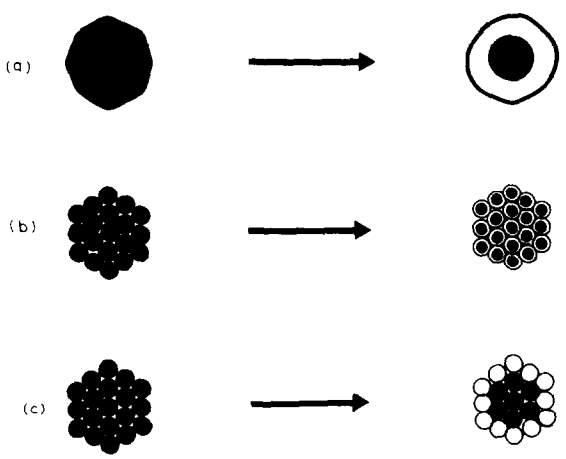

Fig. 1. Chemical conversion of solid particles reacting with a gas to form solid products. (a) Non-porous particle under either chemical or diffusional control (the "shrinking unreacted core" model). (b) Porous particle or agglomerate under chemical control. (c) Porous particle or agglomerate under diffusional control (the "shrinkage unreacted core" model. Key: ●, unreacted material; ○, reacted material.

Porous solid systems consist of agglomerates of individual non-porous particles interspersed with voids to a degree dependent on the porosity of the agglomerate. With porous solids, the pattern of chemical conversion depends on whether the reaction is chemically- or diffusion-controlled. If the former, the concentration of gaseous reactant becomes uniform throughout the solid, and conversion occurs uniformly throughout the particle rather than at a sharp boundary (Fig. 1b). If the reaction in a porous solid is diffusion-controlled (Fig. 1c), conversion is similar to that found with diffusion-controlled non-porous shrinking core solids (Fig. 1a).

Materials and Methods

Materials

Dapsone [1] (DDS) had a mean diameter less than 30 μm. Acetic anhydride [2], sodium phosphate monobasic [2], sodium phosphate dibasic anhydrous [2], glacial acetic acid [3], and acetonitrile [4] (Omni-solv grade) were used as received. Reference samples of monoacetyldapsone (MADDS) and diacetyldapsone (acedapsone, DADDS) were generously provided by Dr. J.H. Peters (SR International, Menlo Park, CA) and Dr. E.F. Elslager (Warner Lambert, Ann Arbor, MI), respectively.

Preparation of DDS particles of controlled size

Precipitated DDS particles were prepared by dissolving DDS powder (50 g) in 40% ethanol (2 liters) at 75°C. The solution was placed in a freezer at −10°C for 12 h, whereupon the cuboidal crystals were recovered by filtration. The crystals were washed with cold water, dried at 40°C and

[1] Aldrich Chemical Co., Milwaukee, WI 53201, U.S.A.
[2] Mallinkrodt, Paris, KY 40361, U.S.A.
[3] Fisher Scientific, Fair Lawn, NJ 07410, U.S.A.
[4] MCB Manufacturing Chemists, Cincinnati, OH 45212, U.S.A.

screened using standard sieves and a Tyler mechanical shaker. The particle size ranges of the resulting fractions were confirmed using an optical microscope.

Compressed DDS particles were prepared by compressing a known weight of DDS powder in a 1.6 cm diameter flat-faced tablet punch and die using a Carver Model B press at a force of 10,000 lb. The resulting solid disc was removed from the die, lightly ground by hand in a mortar and pestle and classified using standard sieves and a Tyler mechanical shaker. Confirmation of the particle size range of each fraction was undertaken using either a microscope or a Coulter Counter, Model T_{AII}.

Reaction of DDS particles

Known weights of either precipitated or compressed particles lying within selected size ranges were placed in a 40-mesh wire basket of the type used in the U.S.P. XX Dissolution Test (Apparatus 1). The basket had been previously wrapped around on the outside with a single layer of fine linen cloth in order to contain the particles while permitting free permeation of acetic anhydride. The basket was connected to a variable speed motor via a metal rod, inserted horizontally into a double-walled, temperature controlled (± 0.5°C) reaction vessel containing acetic anhydride, alone or mixed with glacial acetic acid, and rotated at 25 rpm which was sufficient to set up a tumbling action of the particles. Samples were removed at known time intervals for quantitative analysis of DDS, MADDS, and DADDS. Between 2 and 4 replicates were run; the coefficients of variation ranged from 3 to 8%.

Dissolution of surface-reacted particles

The assembly and operation of the flow-through dissolution apparatus has been described elsewhere (Yang and Swarbrick, 1986b). A known weight (ca. 5 mg) of compressed particles (90–106 μm) was placed in the cylindrical flow-through cell. The flow rate of the dissolution medium, pH 7.4 buffer solution at 37 ± 0.2°C, was 0.91 ml · min^{-1}. The effluent was collected using a Fractomette 200 fraction collector and analyzed for DDS, MADDS and DADDS as below.

Analysis for DDS, MADDS and DADDS

The surface-reacted particles were assayed for the three sulfones using reverse-phase HPLC. The system consisted of a Model 110A Beckman pump, a Model 7125 Rheodyne injector, a C18 μ-Bondapak column (30 cm × 4 mm i.d. 10 μm) and a Model 220 Chromatronix UV detector set at 280 nm. The mobile phase was water : acetonitrile : acetic acid (1000 : 275 : 25 v/v/v) delivered at 2.0 ml · min^{-1} at room temperature. Under these conditions, the retention times for the reference standards were 5.7 min (DDS), 7.5 min (MADDS) and 9.5 min (DADDS). Quantitative precision was 3.9% or less; the limit of sensitivity for each of the 3 sulfones was 5 ng.

Results and discussion

Representative data for the conversion of compressed DDS particles (104–125 μm) in the presence of acetic anhydride vapor are shown in Fig. 2. Over time, DDS is converted to MADDS and DADDS, the latter product predominating as the reaction continues. Qualitatively similar profiles were obtained for other size ranges of compressed DDS particles.

The results of studies focusing on the effect of particle size and type (compressed vs precipitated) during the early stages (0–6 h) of the conversion reaction are presented in Table 1 for four different size fractions of compressed particles and one size

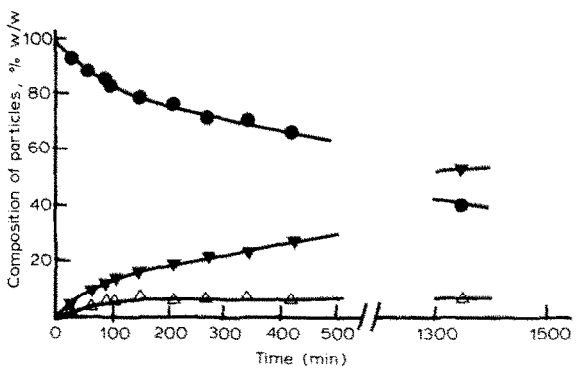

Fig. 2. Chemical conversion of compressed DDS particles (size range 104–125 μm) in the presence of acetic anhydride vapour at 25°C. Key: ●, DDS; △, MADDS; ▼, DADDS.

TABLE 1

EFFECT OF PARTICLE SIZE AND METHOD OF PREPARATION ON THE ACETYLATION OF DDS AT 25°C

Time (h)	Fraction (X) of DDS converted				
	Precipitated particles	Compressed particles			
	82 μm [a]	114 μm	161 μm	228 μm	323 μm
0	0	0	0	0	0
0.5	–	0.069	0.020	0.055	0.039
1.0	0.007	0.119	0.067	0.090	0.045
1.5	–	0.161	–	–	0.069
1.75	–	0.180	–	–	–
2.0	0.027	–	0.125	0.133	0.089
2.5	–	0.213	0.139	0.153	0.103
3.0	–	–	–	–	0.120
3.5	–	0.241	–	–	–
4.0	0.106	–	0.213	–	0.144
4.5	–	0.286	–	–	–
4.75	–	–	–	0.189	–
5.0	–	–	0.234	–	0.158
5.75	–	0.303	–	0.206	–
6.0	0.184	–	0.264	–	0.182

[a] Geometric mean diameter, d_g.

fraction of precipitated particles. It is clear that, at any one time, as the size range of the compressed particles is increased, the fraction (X) of DDS converted to MADDS and DADDS decreases. The time course of the reaction for the precipitated particle sample differs from that of the compressed samples.

For non-porous spherical particles reacting in accordance with the "shrinking unreacted core" model (Fig. 1a), the time course for a chemically controlled reaction is (Szekely et al., 1976):

$$(k_c/r_0)t = 1 - (1 - X)^{1/3} \quad (1)$$

where r_0 is the original radius of the particle and X is the fraction of solid converted at time t. As well as a reaction rate constant, the term k_c contains the equilibrium constant for the reaction and the concentrations of the solid reactant plus gaseous reactants and products.

For non-porous particles undergoing diffusion-controlled reaction (Szekely et al., 1976):

$$(k_d/r_0^2)t = 1 - 3(1 - X)^{2/3} + 2(1 - X) \quad (2)$$

The term k_d in eqn. 2 differs from k_c in eqn. 1 principally in that it contains a diffusion coefficient rather than a reaction rate constant. Eqn. 1 also describes the time course for conversion of porous solids of unchanging size whose reaction is controlled chemically. However, as discussed earlier and shown in Fig. 1b, the reaction with such systems occurs uniformly through the particle rather than at a sharp interface.

The reaction of diffusion-controlled porous solids conforms to eqn. 2 for non-porous solids. While a sharp reaction interface exists as conversion occurs, k_d in this case includes a term to account for the intial porosity of the particle agglomerate; r_o is now the radius of the agglomerate.

Based on the foregoing, the conversion data for the precipitated and compressed particles presented in Table 1 were tested for compliance with Eqns. 1 and 2. The conversion data for all five systems examined are shown in Fig. 3a–e together with the theoretical lines calculated from Eqns. 1 and 2 for chemical and diffusion control, respectively. While the data are not unequivocal, those in Fig. 3a better conform to Eqn. 1 while those of Fig. 3b–e more closely conform to Eqn. 2. This view is supported by the linear regression analyses

TABLE 2

DDS CONVERSION DATA FROM TABLE 1 ANALYZED FOR CONFORMANCE WITH CHEMICAL (Eqn. 1) OR DIFFUSION (Eqn. 2) CONTROL MECHANISMS

Type of DDS particle	d_g (μm)	Chemical control			Diffusion control		
		$(k_c/r_0)t = 1-(1-X)^{1/3}$	r^2	k_c	$(k_d/r_0^2)t = 1-3(1-X)^{2/3}+2(1-X)$	r^2	k_d
Precipitated	82	(0.0014 ± 0.0013) [a] $t + 0.0070 \pm 0.0044$ [a]	0.962	0.468 ± 0.054 [a]	(0.0020 ± 0.0005) [a] $t + 0.0020 \pm 0.0017$ [a]	0.852	3.421 ± 0.822 [a]
Compressed	114	$(0.0187 \pm 0.0022)t - 0.196 \pm 0.0064$	0.915	1.067 ± 0.123	$(0.0066 \pm 0.0003)t + 0.0006 \pm 0.0007$	0.990	21.436 ± 0.813
Compressed	161	$(0.0165 \pm 0.0010)t - 0.0043 \pm 0.0032$	0.980	1.328 ± 0.0078	$(0.0046 \pm 0.0003)t + 0.0024 \pm 0.0009$	0.980	29.870 ± 1.776
Compressed	228	$(0.0116 \pm 0.0018)t - 0.0143 \pm 0.0057$	0.888	1.320 ± 0.209	$(0.0027 \pm 0.0001)t - 0.0003 \pm 0.0004$	0.988	35.624 ± 1.757
Compressed	323	$(0.0103 \pm 0.0006)t - 0.0068 \pm 0.0020$	0.970	1.665 ± 0.104	$(0.0020 \pm 0.0001)t + 0.0009 \pm 0.0003$	0.983	53.297 ± 2.478

[a] Mean $\pm$ S.E.M.

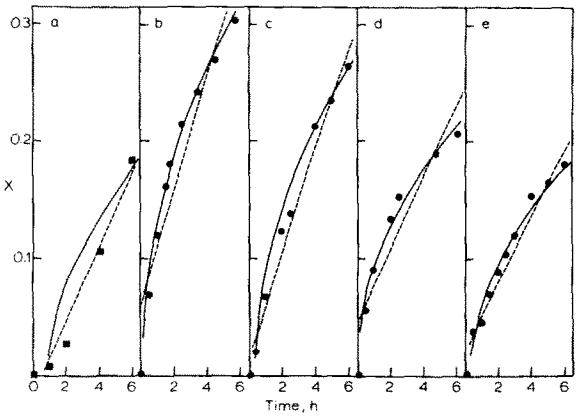

Fig. 3. Effect of particle type (precipitated vs compressed) and size (geometric mean diameter) on the chemical conversion of DDS particles. Key: ■, precipitated, (a) 82 μm; ●, compressed, (b) 114 μm, (c) 161 μm, (d) 228 μm, (e) 323 μm. Relationship predicted by Eqn. 1 (chemical control) shown as - - - - - - and by Eqn. 2 (diffusional control) as ———.

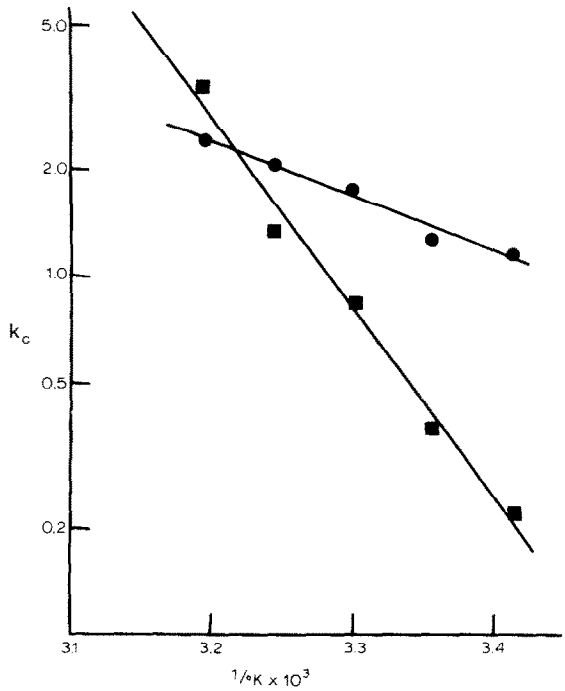

Fig. 4. Effect of temperature on chemical conversion of precipitated (■) and compressed (●) DDS particles ($d_g = 82\mu m$), assuming conformance to chemical control model (Eqn. 1).

shown in Table 2. Together, these findings suggest that the conversion of the precipitated particles is chemically-controlled while that for the compressed particles is diffusion-controlled. Additional evidence for the existence of a difference in reaction mechanism between precipitated and compressed particles comes from the effect of temperature on conversion. The extent of conversion of precipitated and compressed DDS particles (75–90 μm) after 4 h at temperatures ranging from 20 to 40 °C was determined and analyzed in accordance with the Arrhenius equation. Using the approach of Hansen et al. (1966), it was assumed that the precipitated particles were under chemical control; consequently the Arrhenius plot was constructed using k_c (Eqn. 1) versus 1/°K (Fig. 4). The activation energy was calculated as 12.3 kcal/mol. Forcing this same assumption on the compressed particles (Fig. 4) resulted in an energy of activation of 3.5 kcal/mol. Such a value indicates a large diffusional component in the reactivity of these particles.

Szekely et al. (1976) caution against drawing conclusions concerning the mechanism(s) of reaction based on a limited number of studies and when the extent of conversion is relatively small. The possibility exists for both chemical and diffusion control to occur concurrently under certain circumstances. Even so, the results are consistent with the supposition that the particles of the various size ranges prepared by compression are undergoing conversion by a diffusion-controlled mechanism. Irrespective of the degree of porosity in these particles (which must be very small and approaching that for a solid "particle" such as a compressed tablet), this indicates that the acetylation of DDS to MADDS and DADDS follows the "shrinking unreacted core" model. This will produce a well defined layer of reacted product around an unreacted core. A solid system in which the reacted product "coat" is considerably less soluble than the unreacted core is likely to possess modified dissolution characteristics, both in vitro and in vivo. This view is supported by the in vitro dissolution data presented on Fig. 5, which are typical of a large number of dissolution studies conducted using particles of different type, size and extent of surface reaction. It is apparent that for particles of the same type and size, as the extent of surface reaction increases the rate of

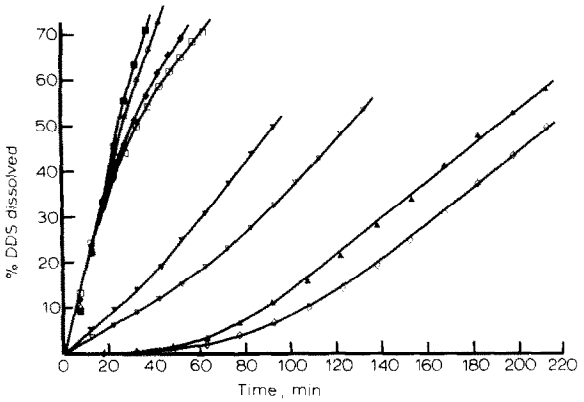

Fig. 5. In vitro dissolution at 37°C and flow rate of 0.91 ml·min^{-1} of DDS particles (90–106 μm) surface-reacted to various extents. Composition of particles are shown below.

Symbol	%DDS	%MADDS	%DADDS
□,◆	100	0	0
△	50.6	31.9	17.5
■	40.1	37.4	22.9
▼	52.8	14.4	32.9
▽	50.5	13.1	36.5
▲	48.0	12.7	39.4
◇	44.9	12.6	42.6

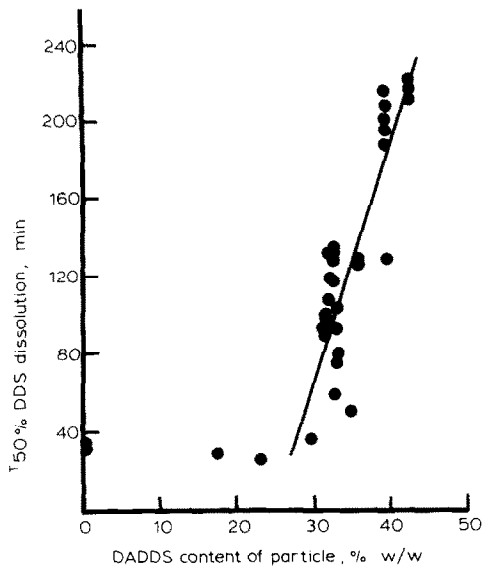

Fig. 6. Effect of DADDS content of surface-reacted compressed particles (90–106 μm) on $T_{50\%}$, the dissolution half-life of the unreacted DDS core. The solid line is based on linear regression analysis of 29 samples containing 30% or more DADDS.

DDS release from the particles decreases, once the conversion reaction has proceeded beyond a certain point. It is reasonable to assume that this effect is due primarily to the presence of the relatively insoluble DADDS derivative in the reacted layer. This is more obvious from Fig. 6, which shows the relation between the dissolution half life ($T_{50\%}$) and the percent DADDS formed during the surface reaction. From Fig. 6, it would appear that approximately 30% DADDS needs to be formed before the $T_{50\%}$ begins to increase. This suggests that below 30% DADDS, the thickness and/or completeness of the reacted surface coat is inadequate to exert a sustaining effect on DDS release. Above 30% DADDS there is a marked effect on DDS dissolution, with the $T_{50\%}$ increasing linearly ($r = 0.838$) with DADDS content. Thus, by careful control of the extent of surface reaction, it is possible to significantly reduce the rate of dissolution of the unreacted core of DDS. As such, this approach may be advantageous in controlling the in vivo release of biologically active compounds. These studies will be the subject of a future publication.

Acknowledgements

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References

Chien, Y.W., Novel Drug Delivery Systems, Marcel Dekker, New York, 1982.

Deasy, P.B., Microencapsulation and Related Drug Processes, Marcel Dekker, New York, 1984.

Ellard, G.A., Pharmacological aspects of the chemotherapy of leprosy. Leprosy Rev., 46 (Suppl.) (1975) 41–51.

Elslager, E.F., New Perspectives on the chemotherapy of malaria, filariasis, and leprosy. In Jucker, E. (Ed.), Progress in Drug Research, Vol. 18, Birkhauser, Basel, 1974, pp. 99–172.

Glazko, A.J., Dill, W.A., Montalbo, R.G. and Holmes, E.L., A new analytical procedure for dapsone. Am. J. Trop. Med. Hyg., 17 (1968) 465–473.

Hansen, J.P., Rushton, T.N. and Khalafalla, S.E., Reduction of ferrous oxide (wustite) at high temperatures. U.S. Bureau of Mines, Report of Investigations 6712, 1966.

Juliano, R.L., Drug Delivery Systems, Oxford University Press, New York, 1980.

Lammintausta, K., Kangas, L. and Lammintausta, R., The pharmacokinetics of dapsone and acetylated dapsone in serum and saliva. Int. J. Clin. Pharmacol. Biopharm., 17 (1979) 159–163.

Modderman, E.S.M., Huikershoven, H., Zuidema, J., Leiker, D.L. and Merkus, F.W.H.M., Intramuscular injection of dapsone in therapy for leprosy: a new approach. Int. J. Clin. Pharm. Ther. Toxicol., 20 (1982) 51–56.

Murray, J.F. Gordon, G.R. and Peters, J.H., A chromatographic-fluorometric procedure for the determination of nanogram quantities of antileprotic sulfones, J. Lab. Clin. Med., 78 (1971) 464–471.

Peters, J.H., Murray, J.F., Gordon, G.R., Levy, L., Russell, D.A. Scott, G.C., Vincin, D.R. and Shepard, C.C., Acedapsone treatment of leprosy patients: response versus drug disposition. Am. J. Trop. Med. Hyg., 26 (1977) 127–136.

Robinson, J.R., Sustained and Controlled Release Drug Delivery Systems, Marcel Dekker, New York, 1978.

Roche, E.B., Design of Biopharmaceutical Properties through Prodrugs and Analogs, American Pharmaceutical Association, Washington, DC, 1977.

Shepard, C.C., Ellard, G.A., Levy, L., Opromolla, V. de A., S.R., Peters, J.H., Rees, R.J.W. and Waters, M.F.R., Experimental chemotherapy in leprosy, Bull. WHO, 53 (1976) 425–433.

Sinkula, A.A., Methods to achieve sustained drug delivery. The chemical approach. In Robinson, J.R. (Ed.), Sustained and Controlled Release Drug Delivery Systems, Marcel Dekker, New York, 1978, pp. 411–555.

Stella, V.J., Mikkelson, T.J., Pipkin, J.D., Prodrugs: the control of drug delivery via bioreversible chemical modification. In Juliano, R.L. (Ed.). Drug Delivery Systems, Oxford University Press, New York, 1980, pp. 112–176.

Swarbrick, J., Prolonged Action Drug Formulation, U.S. Patent No. 4, 461, 776, 1984.

Swarbrick, J. and Ma, D., In vitro dissolution of dapsone, J. Pharm. Pharmacol., 31 (1981) 787–789.

Szekely, J., Evans, J.W., and Sohn, H.Y., Gas-Solid Reactions, Academic Press, New York, 1976, pp. 65–175.

Yang, T.T. and Swarbrick, J., Sustained-release delivery systems. I: Phase diagram studies of dapsone and selected derivatives. J. Pharm. Sci., 75 (1986a) 53–56.

Yang, T.T. and Swarbrick, J., Sustained-release delivery systems. II: In vitro dissolution of 4,4′-sulfonylbisbenzamine (dapsone)-N-dodecyl-4,4′-sulfonylbisbenzamine comelts. J. Pharm. Sci., 75 (1986b) 264–270.