(intrinsic) per °C (Leo & others, 1971). Care must be exercised, however, in applying this statement. Firstly, for compounds with small absolute values of log P, the difference between the *in vitro* values (usually determined at room temperature) and the *in vivo* magnitude at 37° can lead to a large error for the purpose of quantitative *in vitro—in vivo* correlations Secondly, many compounds of medicinal interest have pKa values with temperature dependences (Ballard, 1974) that can have a profound effect on the proportion of their most lipophilic forms present, and thus on partitioning results. Such effects have been reviewed by Ballard (1974). Recently, temperature dependence of partition coefficients has been reported by Kaufman, Semo & Koski (1975), Davis, Elson & others (1976) and Dearden (1976).

Finally, in view of the complex ionization scheme (Leeson & others, 1963) and partitioning behaviour (Colaizzi & Klink, 1969) of tetracyclines, it would be rather tedious to extract thermodynamic values of the relevant physicochemical parameters for the purpose of correlating these quantitatively with biological activity of these compounds. We suggest that, instead, the apparent partition coefficients of tetracycline and its analogues should be measured under conditions closely resembling the biological activity studied.

The tetracyclines for this study were generously supplied by Pfizer Ltd., U.K. October 14, 1976

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The effects of solubility and method of drying on the drug content of various size fractions of tablet granules

HILARY WHITAKER, M. S. SPRING*, *Department of Pharmacy, University of Manchester, Manchester M13 9PL, U.K.*

Variations of drug content of different size fractions of granules have been reported (Lachmann & Sylwestrowicz, 1964; Cox, Ambaum & Wijnand, 1968; Travers, 1974; Selkirk, 1976). These variations have been considered to be due to solvent migration during drying, and abrasion of the granule surface during subsequent handling. We find that this is an insufficient explanation of some results we have obtained.

To examine the effects of the solubility of the minor component and the method of drying, a series of 1 kg batches of granules were made using lactose B.P. (Whey Products Ltd.) as diluent and either sulphanilamide (ICI) or sulphacetamide sodium (Ward Blenkinsop) as drug. The damp granules were divided into two sub-batches and then dried using either a fluid-bed drier or a standard laboratory oven with a fan. A 100 g sample of each sub-batch of dried granules was sieved, and one coarse and some fine sieve fractions were assayed for drug content.

* Correspondence.

Preparation of granules. The granules were made by one of two methods. In method 1, the component powders were screened together. For the 0·02 and 1% levels of sulphacetamide sodium, and the 0·02% level of sulphanilamide, the required weight of drug for a 1 kg batch was dissolved in 120 ml of the binder solution, 5% w/v aqueous polyvinylpyrrolidone (K29-32Gaf). For sulphanilamide 1 and 2%, drug equivalent to 0·02% was dissolved in the binder solution and the remaining sulphanilamide was mixed with the lactose in a Morton Z blade mixer for 2 min before binder was added. The binder (plus drug) was added in two 60 ml portions with 1 min massing between additions; there was a further 5 min massing following the addition of the second portion of the binder. The damp mass was forced through a 1·0 mm screen using a Jackson-Crockatt granulator and divided into 4 portions by quartering. Two opposite quarters were combined for fluid bed drying at 50° for 25 min and one quarter was placed in an enamel tray (20 cm × 30 cm) for oven drying at 50° for 90 min. The dried granules, which had

Table 1. *Percentage of granule in each sieve fraction.*

	Sulphanilamide				Sulphacetamide sodium					
	0·02%		1%		0·02%		1%		2%	
A	O	FB	O	FB	O	FB	O	FB	O	FB
> 1·0	35·8	31·9	31·1	29·7	22·8	17·4	42·2	32·8	—	—
710–1·0	35·8	38·3	36·1	37·3	31·6	26·3	27·9	26·0	—	—
500–710	9·5	8·8	7·2	8·0	9·4	7·7	6·6	6·2	—	—
355–500	4·6	4·2	4·1	3·9	6·1	5·1	4·9	4·8	—	—
250–355	4·2	3·9	4·3	3·9	6·9	6·0	4·9	6·0	—	—
180–250	3·1	3·5	3·9	3·9	6·3	7·6	3·9	6·0	—	—
75–180	4·9	6·7	8·5	8·5	12·7	22·2	6·8	13·3	—	—
< 75	2·1	2·7	4·7	4·9	4·9	7·7	2·9	3·0	—	—
B										
> 710	72·8	78·3	70·5	65·3	80·9	78·4	75·2	71·2	69·3	77·8
53–710	25·5	20·3	27·8	32·8	17·5	20·6	22·8	27·0	27·9	20·3
< 53	1·7	1·4	1·7	1·9	1·6	1·0	2·0	1·8	2·8	1·8

O Oven dried. FB Fluid bed dried. A drug in binder solution. B drug in powder.

Table 2. *Amount of drug in the size fractions of granules expressed as a ratio of the amount of drug in the unfractionated granules.*

	Sulphanilamide				Sulphacetamide sodium					
	0·02%		1%		0·02%		1%		2%	
A	O	FB	O	FB	O	FB	O	FB	O	FB
710–1·0	1·02	0·91	1·01	0·98	1·16	1·08	0·98	1·01	—	—
250–355	1·42	1·42	1·03	1·03	1·61	1·39	1·02	1·09	—	—
180–250	1·42	1·39	1·01	1·03	1·39	1·31	0·95	1·07	—	—
75–180	1·55	1·30	0·89	0·97	1·13	1·28	0·82	0·99	—	—
< 75	2·04	1·47	0·81	0·96	1·29	1·51	0·67	0·83	—	—
B										
> 710	0·99	0·96	1·02	1·02	1·00	0·92	1·02	1·03	1·01	1·00
< 53	1·3	1·08	0·80	0·88	1·06	1·56	0·67	0·87	0·72	0·90

O Oven dried. FB Fluid bed dried. A drug in binder solution. B drug as powder.

a residual moisture content of about 1% w/w, were screened through a 1·4 mm screen. A sample was then subjected to sieve analysis, the results of which are given in Table 1.

Method 2 was essentially the same except that the drugs were added to the lactose as dry powders. In the cases in which 0·02% drug was used the drug was mixed with 10 g of lactose by hand, using a pestle and mortar, before transferring to the Z blade mixer and pre-mixing for 4 min before adding the binder solution. These granules were sieved into 3 fractions (Table 1).

The sieved fractions of granules prepared by both methods were analysed for drug content, and the results are presented in Table 2.

The various granule batches all had similar size distributions, with most being coarser than 710 μm, the only exception being the 0·02% sulphacetamide sodium granules, made by method 1 which were rather finer than the others. The finest size fraction was either deficient in, or enriched with, the minor component. The enrichment was found with 0·02% concentrations of both drugs, and at the 1 and 2% concentrations the finest granules were drug-deficient in every case. This deficiency was greatest for the oven dried granules. Whether the drug was very soluble in water, (sulphacetamide sodium 1 in 1·5), or slightly soluble, (sulphanilamide 1 in 250), these deficiencies were similar in magnitude (Table 2).

Solvent migration followed by abrasion is not a sufficient explanation for these results. It may be that at very low concentrations the drug, being totally soluble in the binder solution, remains preferentially in the crystal bridges between particles, and that these contribute mainly to the fines when the granules are dried.

Conclusions. From the limited data reported here the solubility of drugs in the binder solution has little or no effect on drug concentration in sieve fractions of granules. However, when the drug is present in very low concentrations it appears at above the mean concentration in the finest (< 75 μm) size fraction. The method of drying has only a small effect on variation of drug concentration for the small batch sizes examined.

September 29, 1976

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