Solute migration in a lactose based granulate dried by fluidization and in a fixed bed

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Migration of soluble drugs and dyes during drying of granulates may be the cause of faults such as tablet mottling and drug deficiency (Armstrong & March 1976; Chaudry & King 1972).

Travers (1975) found that intragranular migration of sodium chloride in a kaolin based granulate could result in the loss of about 4% of the marker during fluidization. He attributed this to the abrasion of a solute-rich surface layer. Although there was wide variation in granule size, there was little variation in the solute content of the coarser sized fractions although the fine dust was enriched. Whittaker & Spring (1977) have reported pronounced variation in the coarser sized fractions of a lactose based granulate containing either sulphanilamide or sulphacetamide sodium as solutes. They conclude that some mechanism other than solute migration must be responsible. Selkirk (1976) has presented evidence that migration of soluble lactose can result in a depletion of the granule surface with respect to active ingredients and it is well known that polyvinylpyrrolidine (PVP), which Whittaker & Spring used as a binder, will also migrate to the surface (Ridgway & Rubenstein 1971).

We have studied the migration of sodium chloride in a lactose-based granulate and experimental details, where not given, are as stated by Travers (1975).

200 g portions of previously dried lactose (BDH Chemicals Ltd) were wet massed with 29 ml of a solution of PVP 5% w/w containing either 10 w/w (for 'salt-rich' granules) or 1% w/w of Analar sodium chloride (for 'salt-poor' granules). The wet mass was forced through a 2 800 μm sieve and dried in an Aeromatic laboratory drier for half an hour at 50 °C.

The dried granules and dust from the filter were separated into fractions by sieving a weighed sample

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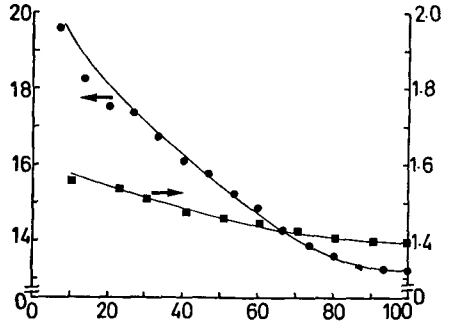

FIG. 1. Solute profiles for granulates dried by fluidization. ● Strong granules ■ Weak granules both retained on a 1680 μm mesh. Ordinate: salt content (mg g^{-1} dry weight). Abscissa: % sample abraded.

Table 1. Solute content of wet massed fractions dried after separation.

Sieve aperture (μm)	Salt content (mg g^{-1} dry solid) Salt-poor granules	Salt-rich granules
2057	1·45	14·5
1680	1·45	14·5
710	1·46	14·5
500	1·45	14·5

which was dissolved and the mean salt content of each estimated by argentimetric titration. The salt-poor granules were titrated using an Orion Ag/S electrode (Model 94–16–00) and multivoltmeter (Model 801) to determine the endpoint (Gran 1952). Samples of wet granules were separated as far as possible and the fractions dried in a vacuum oven at 50 °C. Table 1 demonstrates that these had a uniform salt content which was close to the calculated value.

The solute profiles of granule fractions retained on a 1680 μm mesh sieve are shown plotted in Fig. 1. The results indicate that the salt-rich granules had undergone appreciable intragranular migration which was, however, less than that shown by a kaolin-based granulate (Travers 1975). The salt-poor granules had a shallower profile. This may be due to the concurrent migration of lactose and/or PVP which would 'dilute' the salt deposited near the granule surface. There is a slight but significant increase in the salt content of the dust fractions (Table 2) but this enrichment is relatively less for dust from salt-poor granules. This fact is consistent with the solute profiles and with abrasion of the solute-rich outer layers.

Table 3 gives the mean solute content of granules at various depths in batches dried in a 'split' bed. The pattern of intergranular migration is similar, though less pronounced, to that in the kaolin-based granulate.

Table 2. Solute content of dry granule fractions.

Sieve aperture (μm)	% Retained on stated aperture Salt-poor grans	Salt-rich grans	Salt content (mg g^{-1} dry solid) Salt-poor grans	Salt-rich grans	Kaolin* based grans
2057	26·3	18·8	1·43	14·3	25·0
1680	31·6	45·4	1·45	14·3	25·5
710	6·2	11·5	1·46	14·5	25·5
500	9·5	9·6	1·46	14·5	25·0
355	7·3	3·1	1·45	14·4	25·0
250	4·4	2·7	1·44	14·6	24·4
180	3·9	1·9	1·45	15·0	26·3
150	3·0	1·6	1·46	15·5	29·0
105	—	—	—	—	28·4
75	2·0	1·2	1·47	15·6	—
63	1·4	1·1	1·50	15·6	—
53	1·0	0·7	1·51	16·40	33·5
45	0·8	0·7	1·52	16·6	44·1

*Data from Travers (1975).

Table 3. Solute content of granules dried in a fixed bed.

Mean depth below bed surface (mm)	Salt content mg per g dry solid (1)	(2)	(3)	(4)	(5)	(6)
1·65	1·43	14·2	1·50	15·4	25·1	32·3
4·95	1·45	14·7	1·48	15·1	26·5	27·8
8·25	1·47	15·7	1·47	14·7	30·8	25·5
11·55	1·49	15·5	1·45	14·5	34·0	22·8
14·85	1·40	14·4	1·43	14·3	16·5	22·9
18·15	1·39	13·1	1·42	14·2	7·4	22·2

(1), (2) Beds dried by infrared radiation at peak wavelength 2·8 μm for 60 min.
(3), (4) Beds dried by convection with warm air at 37 °C for 7 days.
(5) Kaolin-based granule dried by infrared as beds (1) and (2) (Travers 1975).
(6) Ditto dried by convection in air at 37 °C for 2 days (Travers 1975).

Each figure is the mean of two determinations under the stated conditions.

We therefore consider that migration effects similar to those operating in the kaolin-based system also account for the solute distribution in these lactose granulates.

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Disappearing *N*-hydroxy compounds

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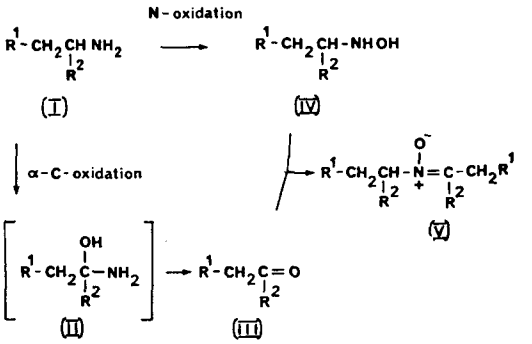
Although metabolic *N*-oxidation of both primary and secondary aliphatic and aromatic amines to give hydroxylamines has been well established (see Weisburger & Weisburger 1973; Coutts & Beckett 1977, for reviews), the presence of these relatively unstable compounds in biological fluids has been questioned. Even when their presence has been demonstrated, it is possible that the amounts present have been greatly underestimated for the following reasons:

Condensation following metabolism. Metabolic oxidation of aliphatic *N*-centres e.g. (Scheme 1) in drugs and endogenous amines involves α-*C*-oxidation yielding ketones (III: R^2 = alkyl) and aldehydes (III: R^2 = H), via alkanolamines (II), as well as *N*-oxidation to give hydroxylamines (IV). Thus compounds (i.e. carbonyl compounds and hydroxylamines) with potential for mutual condensation to produce nitrones (V) are formed by the same general oxidative process in the same biological tissues (Scheme 1).

There is some evidence that either the same active sites or closely associated active sites are involved in both oxidation routes (Beckett 1978). Also since *N*-oxidation and deamination occur in brain tissue (as well as in liver and kidney) such nitrones may be produced locally in the c.n.s. as well as at many other sites.

Under simulated biological conditions and concentrations i.e. in either aqueous phase, e.g. phosphate buffer pH 7·4, or lipid medium e.g. chloroform, we demonstrated that *N*-hydroxydidesmethyl imipramine, -chlorimipramine, -promazine and -chlorpromazine, readily combined with phenylacetaldehyde (the product of deamination of phenethylamine an endogenous amine) and also acetaldehyde, from the metabolic oxidation of ethanol, to give the corresponding nitrones. Also, metabolically-produced primary hydroxylamines of mexiletene, norfenfluramine, amphetamine and phenethylamine condensed with their products of deamination to give the corresponding nitrones. These products were identified by comparison with authentic materials (t.l.c. and m.s. evidence).

Condensation reactions of amines, drugs or endogenous compounds, with aldehydes (derived from various sources) have previously been reported (see Jenner & Testa 1978). For example, dopamine condenses with its deaminated product and with acetaldehyde to give tetrahydropapaveroline and the related alkaloid salsolinol respectively (Scheme 2).



Scheme 1. The metabolic formation of N-oxidation and deamination products with potential for mutual condensation to give nitrones. R^1 = aryl, aralkyl or alkyl; R^2 = alkyl or H; [ ] indicates unstable compounds.

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