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The characterization of drug redistribution in a ternary interactive mixture of diazepam

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Summary

The addition of specially prepared particle size fractions of two disintegrants, Explotab and Starch 1500 to a preformed diazepam-lactose interactive mixture resulted in a redistribution of the diazepam between the lactose and disintegrant carriers; the extent of the redistribution was dependent on the disintegrant's affinity for the diazepam. The application of phase distribution and adsorption isotherm theory to this solid particulate system allowed the redistribution process to be mathematically modelled and empirically characterized by a distribution coefficient and by Freundlich isotherm constants. The distribution coefficient of diazepam between the lactose and the disintegrant carriers was 1.39 ± 0.07 ($P = 0.95$, df = 22) and 0.53 ± 0.08 ($P = 0.95$, df = 13) for Explotab and Starch 1500, respectively. The Freundlich constant, n, characteristic of the absorbate diazepam was not significantly different between the adsorption isotherms for the two disintegrants (1.06 ± 0.11 ($P = 0.95$, df = 22) and 1.14 ± 0.24 ($P = 0.95$, df = 13) for Explotab and Starch, respectively) and was not significantly different from 1.0. This model was therefore mathematically equivalent to the partition model. The affinity of the diazepam for the disintegrants could be characterized by the Freundlich constant k and was 1.57 and 0.36 for Explotab and Starch, respectively.

Introduction

The addition of disintegrants to preformed interactive mixtures has been shown to affect the stability of the system by competing for the drug on the carrier surface causing its redistribution between the disintegrant and carrier (Soebagyo and Stewart, 1985, 1989). Factors influencing the redistribution process have been studied (Soebagyo and Stewart, 1989). Affinity of the drug for the disintegrant, the disintegrant's concentration and particle size, and the carrier's particle size have a major effect on the degree of redistribution and therefore the homogeneity and the potential of the system to undergo segregation. When mixes of increasing diazepam concentration were studied, the percent of diazepam redistribution to the disintegrant remained relatively constant indicating that an equilibrium had been established.

The purpose of this paper is to quantify the redistribution process by the use of mathematical models.

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Experimental

Materials

Diazepam (Alphapharm) was micronized by fluid energy milling (Chrispro Jetmill model 75P, compressed air at 12.7 l s^{-1}; d_{vn} = 3.1 μm, microscopic analysis log normal, geometric standard deviation = 1.46 μm). The carrier was lactose-starch granules (2 : 1, prepared by wet granulation in Erweka laboratory scale equipment using starch paste (10% w/w) as the binder; 250–425 μm fraction obtained from 20 mesh granules by sieve classification). The disintegrants used in the study were Explotab and Starch 1500. Particle size fractions of Starch 1500 was obtained by preliminary compression (Manestry E2 with maximum overload and compression), comminution (Erweka laboratory granulator) and then sieve classification (Pascall sieve shaker with Endecott test sieves, 20 min), and fractions of Explotab by an aqueous granulation (Erweka), comminution (Erweka oscillating granulator) and then sieve classification (Pascall sieve shaker with Endecott test sieves, 20 min). All materials were stored over silica gel in a drying cabinet during the study.

Methods

Diazepam assay Diazepam was assayed spectrophotometrically by shaking the sample containing 0.25–2.00 mg diazepam in 10–20 ml of ethanol (40%) for 30 min to extract diazepam and centrifuging (Hettich Rotanta/RP; 1500 rpm, 20 min) to remove insoluble particles. The concentration of diazepam was measured using a Pye Unicam PU 8600 UV/Vis spectrophotometer with a Pye Unicam automatic sample changer. Beer's Law calibration plots were linear over the concentration range of 5–150 μg ml^{-1} at 315 nm. The lactose carrier and disintegrants showed negligible absorbance at 315 nm in the concentrations used in the study ($A < 0.005$).

Preparation of the mixture Powder mixing of the diazepam-disintegrant and diazepam-lactose mixtures was performed in an Erweka Cube Mixer (20 rpm, load 100–500 g, 60 min). Preparation of the ternary mixtures was performed by mixing in a glass bottle (load 10–35 g) attached to the Erweka Cube Mixer (20 rpm, 30 min).

Evaluation of the degree of homogeneity Homogeneity of the mixtures was evaluated by randomly removing 20 100-mg samples for assay of the drug content using a sample thief to minimize any disturbance to the mix. The degree of homogeneity was expressed by the coefficient of variation.

Separation of lactose and disintegrant interactive units Segregation studies were performed using a Pascall sieve shaker containing Endocott test sieves. The mixture was placed on a 250 μm sieve and subjected to segregation condition for 60 min, i.e., low frequency of vibration (approx. 200 Hz) and high acceleration (of the order of 100 m s^{-2}). The amount of diazepam per 100 mg was determined in the powder samples above and below the sieve after segregation. Either the whole of the powder sample on the sieve (or 10×100 mg samples selected randomly if the amount was too large) was used for the drug analysis.

Results and Discussion

Satisfactory interactive mixes of micronized diazepam (0.01–5.0%) and lactose granules (250–425 μm) were formed after 60 min mixing (CV < 1.6%). The process of drug redistribution was studied by mixing these performed interactive mixtures of diazepam-lactose granules with disintegrants processing high (Explotab) and low (Starch 1500) affinity for diazepam. The disintegrants of different affinities were prepared in 125–150 μm particle size fractions by wet and dry granulation techniques to allow the mechanism of redistribution to be studied (Soebagyo and Stewart, 1989). The affinities of the artificially prepared disintegrants used in this study did not represent the intrinsic affinities of the commercially available materials.

When 5% of the disintegrants was mixed with performed diazepam-lactose interactive mixes of differing diazepam concentrations (0.01–5.0%), good homogeneity of the ternary mixes was achieved, i.e., CVs ranged from 1.1 to 3.4% for Explotab and 1.8 to 2.5% for starch 1500 after 30

TABLE 1

The redistribution of diazepam in a diazepam-lactose granule (250–425 μm) interactive system after mixing of a modified Explotab (125–150 μm) for 30 min

Percent diazepam	Diazepam ratio [a]	W_s (g) [b]	W_c (g) [c]	W_d (g) [d]	W_l (g) [c]	Percent diazepam removed
0.0095	0.965	0.0076 [f]	0.0013	0.0006	0.0089	5.8
0.0475	0.906	0.0357	0.0067	0.0033	0.0425	6.9
0.0950	0.924	0.0729	0.0134	0.0087	0.0863	9.2
0.2375	0.877	0.1730	0.0335	0.0310	0.2065	13.1
0.4750	0.930	0.3670	0.0670	0.0410	0.4340	8.6
0.950	0.921	0.7260	0.1340	0.0900	0.8600	9.5
1.90	0.945	1.490	0.2680	0.1420	1.758	7.5
4.75	0.938	3.698	0.6700	0.3820	4.368	8.0

[a] Ratio of the diazepam concentration above and below the 250 μm sieve.
[b] Weight of diazepam in the 250 μm sieve fraction after the separation process.
[c] Weight of diazepam estimated to pass into the subgranule fraction due to lactose granule comminution and constituent segregation.
[d] Weight of diazepam associated with Explotab.
[e] Weight of diazepam associated with lactose granule during mixing.
[f] All data shown are the average of triplicate determinations.

min mixing. The mixtures were shaken over a 250 μm sieve for 60 min to separate the diazepam-lactose and diazepam-disintegrant interactive unit fractions and the drug associated with each fraction determined by analysis. In addition to diazepam-disintegrant interactive units, the subsieve fraction contained some smaller particle size diazepam-lactose granule units (i.e., less than 250 μm) due to comminution during the vigorous sieve separation process and free diazepam due to constituent segregation. The diazepam content of the comminuted lactose granule and free di-

TABLE 2

The redistribution of diazepam in a diazepam-lactose granule (250–425 μm) interactive system after mixing of a modified Starch (125–150 μm) for 30 min

Percent diazepam	Diazepam ratio [a]	W_s (g) [b]	W_c (g) [c]	W_d (g) [d]	W_l (g) [c]	Percent diazepam removed
0.0095	1.016	0.0082 [f]	0.0013	–	0.0096	–
0.0475	1.019	0.0413	0.0067	–	0.0479	–
0.950	1.004	0.0813	0.0134	0.0002	0.0948	–
0.2375	0.981	0.1987	0.0335	0.0053	2.2322	2.2
0.4750	0.985	0.3991	0.0670	0.0089	0.4661	1.9
0.950	0.962	0.7796	0.1340	0.0364	0.9136	3.8
1.90	0.975	1.5800	0.2680	0.0518	1.8482	2.7
4.75	0.974	3.9460	0.6700	0.1336	4.6164	2.8

[a] Ratio of the diazepam concentrations above and below the 250 μm sieve.
[b] Weight of diazepam in the 250 μm sieve fraction after the separation process.
[c] Weight of diazepam estimated to pass into the subgranule fraction due to lactose granule comminution and constituent segregation.
[d] Weight of diazepam associated with Explotab.
[e] Weight of diazepam associated with lactose granule during mixing.
[f] All data shown are the average of triplicate determinations.

azepam fraction can be estimated by subjecting the same batch of the diazepam-lactose mixture to the same segregation condition that occurred during the sieving process, e.g., $5.5 \pm 0.7\%$ of diazepam was lost from a 0.25% diazepam-lactose binary mixture after sieving for 60 min.

The diazepam distribution after mixing with the disintegrants can be estimated (Tables 1 and 2). During this mixing, the diazepam was redistributed between the lactose carrier and the disintegrant; the degree of redistribution was related to the affinity of the drug for the disintegrant's surface. When 5% of Explotab was mixed with the diazepam-lactose binary mixture, $8.6 \pm 2.2\%$ of the diazepam was removed from the lactose carrier in contrast to only $2.7 \pm 0.7\%$ for the addition of 5% Starch 1500. The process of drug redistribution is illustrated in Fig. 1.

Two approaches were taken to quantify the redistribution process:

(1) The drug affinity was characterized by a 'distribution coefficient' of the diazepam between the lactose and disintegrant solids 'phases'. This data treatment is conceptually similar to the classical partitioning of drugs between two immiscible liquid phases (Glasstone and Lewis, 1962; Martin et al., 1983). Partitioning theory was developed to interpret molecular behaviour and has theoretical limitations for the particulate systems. However, an empirical approach using partition theory to model the redistribution behaviour was pursued. The consideration of the lactose granules and disintegrant particles as different solid phases is reinforced by the different surface characteristics, adhesion sites and chemistry of these interactive units. In a homogeneous random mixture of lactose and disintegrant interactive units, diazepam will distribute between these units in a manner which reflects the drugs affinity for either solid carrier. Such a hypothesis requires that equilibrium conditions have been met, i.e., the mixing process has produced an appropriate envi-

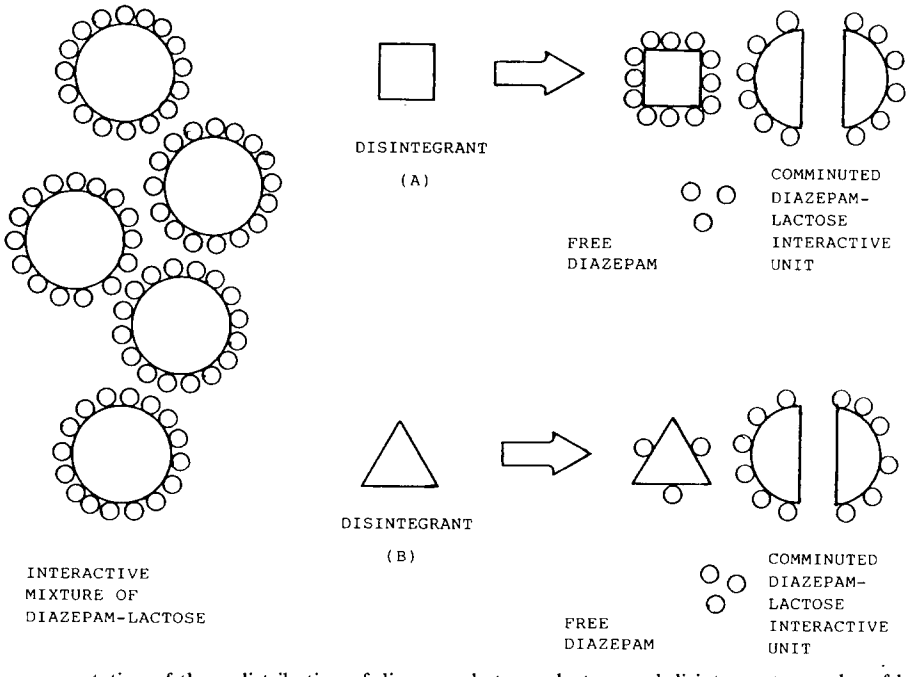

Fig. 1. Schematic representation of the redistribution of diazepam between lactose and disintegrant granules of high (A) and low (B) affinity disintegrants.

ronment for maximizing the interaction processes between diazepam and interactive units. For this system,

$$D_L \rightleftharpoons D_D$$

where D_L is the diazepam concentration in the lactose phase, and D_D denotes the diazepam concentration in the disintegrant phase.

The empirical distribution coefficient K can be defined

$$K = D_D/D_L$$

and will describe the affinity of the drug for the disintegrant.

The mass balance for the redistribution diazepam is as follows:

$$W = W_L + W_D$$

where W, W_L, and W_D are the masses of diazepam associated with the total mixture, lactose granules and disintegrant, respectively. If D, D_L and D_D represent the concentration of the diazepam associated with the mixture, the lactose granules and disintegrant in mg g^{-1}, and M, M_L and M_D are the masses of the total mixture, lactose granule and disintegrant (g), respectively, then:

$$DM = D_L M_L + D_D M_D$$

$$D_L = (DM - D_D M_D)/M_L$$

Thus

$$K = D_D M_L/(DM - D_D M_D)$$

and

$$D_D = KMD/(M_L - KM_D)$$

Diazepam concentrations associated with the lactose mixture and disintegrants can be calculated from the data in Tables 1 and 2. A plot of D_D vs. D should be linear and the distribution coefficient (K) can be determined from the slope (Fig. 2). Reasonable linearity is displayed (analysis of variance showed no significant difference from linearity for both Explotab and Starch) and the slop of the lines provide distribution coefficients of 1.39 with a confidence interval of 0.07 ($P = 0.95$, df = 22) and 0.53 with a confidence interval of 0.07 ($P = 0.95$, df = 13) for Explotab and Starch, respectively. The assumptions made in this modelling procedure include (a) that the diazepam distribution process can be characterized by a one compartment equilibrium defined above, i.e., diazepam is associated only with the lactose and disintegrant interactive units and does not occur as free particles in the mixture, (b) that the redistributive process has reached equilibrium and (c) that the solid phases have not been saturated with drug. Some credibility can be given to these assumptions since the microscopic examination of this powder system after the redistributive mixing process using scanning electron microscopy revealed little free drug, and the low coefficients of variation of the ternary mixes are indicative of interactive powder mixes where further mixing has little effect on drug homogeneity.

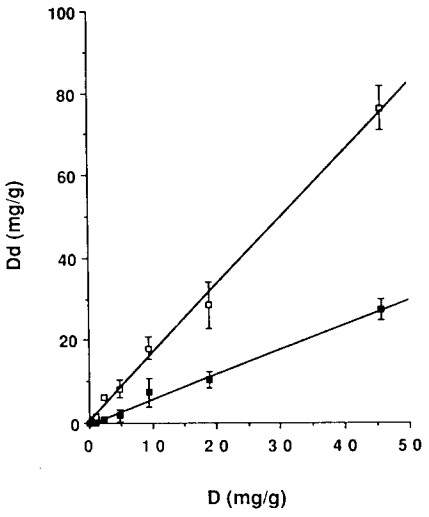

Fig. 2. Plot of the concentration of diazepam associated with the disintegrant vs the initial diazepam concentration after drug redistribution from a lactose interactive mixture. (□) Explotab, (■) Starch 1500.

(2) The competitive drug redistribution process can be considered analogous to an adsorption or ion-exchange process where the drug is

the absorbate and the disintegrant is the adsorbent. The equilibrium may be represented

$$Dr + D \rightleftharpoons DrD$$

where Dr represents the diazepam associated with the lactose and is analogous to the drug in solution, D is the disintegrant and DrD is the drug associated with the disintegrant.

In gaseous and solution systems, the adsorption process can be characterized by various types of isotherms (Glasstone and Lewis, 1962; Martin et al., 1983). This quantification approach was extended to these solid systems; however, the approach must be considered empirical as the adsorption process in gas and solution is molecular and isotherms have been developed for adsorbed layers which are only a few molecules in thickness.

The use of the more empirical Freundlich isotherm was employed to quantify the redistribution, i.e.

$$\log D_D = \log k + n \log D$$

where D_D denotes the amount of diazepam absorbed per unit mass of disintegrants (mg g^{-1}) from a solid system of diazepam concentration D (mg g^{-1}) and k and n are constants for the disintegrant and diazepam, respectively.

The data fit this isotherm reasonably well with linearity being achieved for both disintegrants, i.e., an analysis of variance showed no significant departure from linearity for both Explotab and starch (Fig. 3).

The constants k and n can be used to characterize the redistribution process. The similar values of n obtained from the slope of the regression (i.e., 1.06 ± 0.11 ($P = 0.95$, df = 22) and 1.14 ± 0.25 ($P = 0.95$, df = 13) for Explotab and Starch, respectively) were consistent with the same absorbate diazepam being used in both isotherms. The constant k was calculated from the intercept as 1.53 and 0.36 for Explotab and Starch 1500, respectively, and can be used to discriminate between different interaction capacities of the disintegrants, i.e., the higher value of k for Explotab demonstrated its higher affinity for the diazepam.

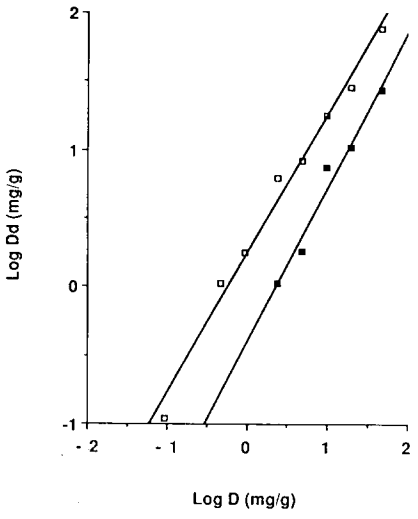

Fig. 3. Freundlich isotherm for the adhesion of diazepam onto disintegrants from a solid interactive diazepam-lactose system. (□) Explotab, (■) Starch 1500.

The confidence limits of n for both disintegrants embraced the value of 1.0 and so the Freundlich equation reduced to the expression $D_D = k \cdot D$ which was the same as the partition model. The values of the partition coefficient (K) and the Freundlich constant k were therefore similar.

In testing the models, the concentration term for drug in each of the solid phases was expressed as weight of drug per weight of solid phase. The distribution coefficients and the adsorption isotherm constants must be interpreted on this basis. Ideally, a concentration term which would reflect surface capacity is required in the same manner as weight per unit volume would be used in a conventional drug distribution study to reflect the degree of saturation in solution. Surface capacity in the solid systems is related to the number of adsorption sites on the particulate surface which will depend on available surface area, surface characteristics like roughness and porosity, and pore volume distributions. In addition, the surface capacity will be dependent on the particle characteristics of the adsorbed drug. The use of a concentration term like weight per surface area may seem more attractive but still suffers from many of the same disadvantages as

weight per weight. Samples of differing surface areas may not reflect the adhesion capacity in particulate systems because available adhesion sites may not change proportionally. For example, increase in surface area due to fine pores in a sample may not provide increased adhesion sites because the drug may not be accessible to these areas; increase in surface area may not increase the adhesion sites proportionally because the electrical charging properties of the material may be changed. In view of this, weight per weight concentration terms have been used throughout this paper; further studies are required to resolve these problems.

Conclusion

Two models have been applied to solid particulate systems in order to determine the affinity of a drug diazepam for disintegrants which were added to a preformed interactive system. Given the inherent variability within particulate systems, relatively good data fits were obtained from the partition and Freundlich models to characterize the redistribution of diazepam between a lactose granule carrier and two disintegrants Explotab and Starch. Assumptions have been made in the application of this theory to particulate systems and research will continue to validate these assumptions and to extend the studies to other drugs and carriers. The ability to model solid interactions in this manner will have application in the rational design and development of interactive drug systems.

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