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Factors influencing the homogeneity and drug redistribution of disintegrant-diazepam-carrier ternary mixtures

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Summary

The homogeneity and diazepam redistribution in ternary mixtures consisting of diazepam-lactose interactive units and randomly mixed disintegrants were studied during mixing and under segregation conditions. Modified disintegrants of differing particle size fractions (micronized up to 180 μm) and diazepam affinities (0.195–1.00%) were prepared by wet and dry granulation and sieve classification. The randomly mixed disintegrants competed for the diazepam adsorbed on the lactose carrier to form separate interactive units; the extent of diazepam removal from the carrier surface increased with the higher affinity disintegrants. Increased disintegrant concentrations caused significant stripping of the diazepam from the lactose carrier when the disintegrant possessed a high affinity for the drug, i.e. the redistribution ratio decreased from 0.916 to 0.692% over a 1 to 20% disintegrant range. When mixes of increasing diazepam concentration (0.01 to 5.0%) were prepared, the redistribution ratio was relatively constant indicating that an equilibrium redistribution had been established. Larger particle size diazepam-lactose interactive systems were less stable to segregation with constituent segregation of the diazepam occurring in addition to the competitive redistribution caused by the high affinity disintegrants.

Introduction

The addition of a disintegrant to a preformed prednisolone interactive mixture was shown to produce a redistribution of the drug between the carrier and disintegrant causing potential drug segregation in the ternary system (Soebagyo and Stewart, 1985). As the disintegrant did not interact with the carrier, its addition to the binary interactive mixture produced initially a system consisting of a random mixture of interactive drug carrier units and disintegrant particles. During subsequent blending, the drug redistributed in the system to varying degrees depending on its relative affinity for the carrier and disintegrant.

The aim of this research was to investigate some of the factors which might influence the extent of the redistribution process. This paper therefore reports on the effect of modified commercial disintegrants' particle size and concentration, the drug concentration, and the carrier's particle size on the homogeneity and drug redistribution of a diazepam-lactose granule interactive system. The research addresses ternary systems in which the modified disintegrant possesses both high and low affinity for the diazepam.

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Experimental

Materials

Diazepam (Alphapharm) was micronized by fluid energy milling (Chrispro Jetmill model 75P, compressed air 5.8 atm at 12.7 l s^{-1}; d_{vn} = 3.1 μm, microscopic analysis, log normal, geometric standard deviation = 1.46). 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 Polyplasdone XL, Explotab, Avicel and Starch 1500. Particle size fractions of Polyplasdone XL were obtained directly by sieve classification (Pascall sieve shaker, Endecott test sieves, 20 min). Particle size fractions of Avicel and Starch 1500 were obtained by preliminary compression (Manesty 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 g 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 twenty 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.

Affinity and segregation studies. Affinity and segregation studies were performed using a Pascall sieve shaker containing Endecott test sieves. The mixture was placed on a sieve having an aperture equivalent to the carrier's lower size limit and subjected to segregation condition for 60 min, i.e. low frequency of vibration (200 Hz approx.) 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

Affinity of diazepam for the disintegrant

Diazepam was mixed with two size fractions of the artificially modified disintegrants to give interactive mixtures of satisfactory homogeneity (CV values were below 5%; Table 1). The affinity of the diazepam for the disintegrants was determined by subjecting sieves containing the preformed diazepam-disintegrant interactive mixture to accelerative vibratory conditions on a sieve shaker (i.e. low frequency of vibration, high acceleration (Staniforth and Rees, 1982, 1983) and for 60 min) and the degree of diazepam segregation of these mixtures determined by analysis of sample above and below the sieve. It was inappropriate to define drug affinity to the carrier by the percent of drug passing through the sieve since the comminuted fraction of the carrier containing adhered diazepam inflated the diazepam concentration in the below sieve fraction. The affinity therefore was

TABLE 1

Homogeneity and affinity of diazepam (0.25%) in interactive mixtures with modified disintegrants

Disintegrant	CV (%)[a]	Affinity[b]	Weight[c] retained
Explotab (150–180 μm)	0.6	1.000	99.5
(106–125 μm)	0.6	0.955	98.3
Polyplasdone XL (150–180 μm)	0.7	0.973	79.2
(106–125 μm)	1.8	0.983	95.9
Starch 1500 (150–180 μm)	4.4[d]	0.802	99.8
(106–125 μm)	4.6[d]	0.456	98.7
Avicel PH101 (150–180 μm)	3.7	0.490	95.0
(106–125 μm)	1.7[d]	0.195	92.7

[a]30 min mixing time.
[b]Ratio of the concentration of diazepam above and below the sieve.
[c]Weight of mixture retained on the sieve representing the friability of the particles in the mixture.
[d]60 min mixing.

characterized by the ratio of the diazepam concentrations above and below the sieve (Table 1). The results indicated that the modified Explotab and Polyplasdone XL possessed a high affinity for diazepam, while the drug was weakly bound to Starch 1500 and Avicel. The drug loss from the disintegrant was mainly due to constituent segregation as the comminution of the disintegrant particles during the sieving process was minimal (i.e. 0.5–7.3% passed through the sieve) with the exception of the large size fraction of Polyplasdone (20.8% passed through the sieve). These results were consistent with the homogeneity data in Table 1 which shows that the low affinity disintegrants produced the less homogeneous diazepam mixes and took longer times to mix due to the formation of partial interactive mixtures (Thiel, 1984) consisting of free diazepam and disintegrant particles and diazepam-disintegrant interactive units. The particle size of the disintegrants influenced their affinity with larger particle size fractions showing a higher affinity. Previous research has observed particle size segregation dependence of binary mixtures caused probably by differences in the carrier's surface porosity and roughness (Rees and Staniforth, 1979; Schmidt et al, 1984). The affinity of the diazepam for the lactose carrier (250–425 μm) was determined to be 0.909.

The methods of producing the particle size fractions of the disintegrants will change the characteristic of original materials, especially the surface properties. Therefore, the affinities of the modified disintegrants used in the study may not represent the true affinity of the commercial disintegrants; however, the use of such methodology was important in characterizing the mechanism of segregation.

Effect of particle size of ternary disintegrants

The addition of modified disintegrants (5%) in different particle size ranges (e.g. 150–180, 106–125, 45–63 μm and micronized) to the preformed 0.25% diazepam-lactose granule 250–425 μm interactive mixture (CV = 1.6%) produced homogeneous ternary mixtures after mixing for 30 min, i.e. all the CVs were less than 5% (Table 2). The presence of non-micronized fractions of Polyplasdone XL and Explotab showed slight increases in the diazepam CV's whereas low affinity disintegrants, Avicel and Starch 1500 produced mixes of excellent homogeneity (i.e. CV 0.7–1.0%). The homogeneity of the ternary mixtures decreased when the diazepam underwent the greatest degree of redistribution onto the added disintegrant, i.e. the achievement of homogeneity in a mix consisting of drug depleted diazepam-lactose interactive units and disintegrant particles containing the redistributed diazepam was more difficult than in a mix of diazepam-lactose interactive units and relatively drug free disintegrant particles. The rea-

sons for the homogeneity changes cannot be definitively explained but was probably associated with the extent of interactive unit segregation of the differing particle size fractions of the diazepam-lactose and diazepam-disintegrant units and their relative diazepam contents.

Segregation studies were performed using a Pascall sieve shaker containing a 250 μm sieve. This sieve size was between the lower limit of the carrier size (250–425 μm) and the modified disintegrant size fraction (150–180, 106–125, 45–63 μm and micronized). This method allowed the separation of the disintegrant from the diazepam-lactose interactive units, and therefore allowed the determination of the degree of drug redistribution between carrier and ternary material.

The degree of redistribution of diazepam in the mixtures of 0.25% diazepam-lactose granule 250–425 μm-5% disintegrant was characterized by the ratio of the diazepam concentrations above (associated with the lactose granule) and below (associated with the disintegrant and comminuted lactose granules) the sieve and was significantly different in both disintegrant type and particle size fraction (Table 2; F-test; $p = 0.05$). The degree of redistribution of the mixtures depended on the particle size and diazepam affinity for the disintegrant.

The addition of micronized fractions of ternary disintegrants stabilized most of the mixtures against diazepam segregation. Scanning electron microscopy confirmed the adhesion of the micronized disintegrants showing some interaction of these powders with the surface of the diazepam-lactose adhesion unit. The micronized disintegrants seem to have affected the stability of the mixture in the same way as the cohesive lubricants (Stewart, 1981; Soebagyo and Stewart, 1985). The effect of the micronized high affinity disintegrants, Polyplasdone XL and Explotab showing ratios of 0.928 and 0.970 respectively confirm their poor drug stripping power.

The larger particle size fractions of high affinity Polyplasdone XL and Explotab caused the greatest diazepam redistribution with the redistribution ratios ranging from 0.758 to 0.945 for the non-micronized disintegrant fractions (Table 2). Scanning electron microscopy confirmed that the larger particle size fractions of Polyplasdone XL and Explotab did not interact with the surface of the

TABLE 2

Homogeneity and degree of drug redistribution in a mix of 0.25% diazepam-lactose interactive system (250–425 μm) with 5% modified disintegrant

Disintegrant		150–180[a]	106–125	45–63	10
Polyplasdone XL	CV[b]	3.3	4.6	4.2	1.3
	R[c]	0.827	0.779	0.758	0.928
	W[d]	92.3	91.0	93.9	93.1
Explotab	CV	3.0	2.9	1.4	0.8
	R	0.889	0.876	0.945	0.970
	W	86.5	87.1	86.8	85.6
Avicel	CV	0.7	0.8	1.0	0.8
	R	0.976	0.989	0.982	0.955
	W	85.2	85.3	85.6	87.7
Starch 1500	CV	1.0	0.9	0.7	0.9
	R	0.985	0.981	0.960	0.990
	W	86.4	87.4	86.7	87.1

[a]Particle size fractions of disintegrants in μm.
[b]CV is the coefficient of variation of the mix after 30 min mixing.
[c]R is the diazepam redistribution ratio and is the ratio of the diazepam concentration above and below the sieve.
[d]W is the percent of mix by weight remaining on the sieve.

adhesion unit. These disintegrant particles competed for the diazepam in the diazepam-lactose interactive system to produce Polyplasdone XL-diazepam and Explotab-diazepam interactive units. By comparison, Starch 1500 and Avicel which possessed a lower affinity for the drug removed little of the diazepam from the diazepam-lactose system during the segregation process (Table 2). The redistribution ratios for the Avicel and Starch 1500 ternary system were significantly higher than of the Explotab and Polyplasdone XL ternary system (F-test; $p = 0.05$) for the non-micronized particle size fractions.

The presence of disintegrants in the binary interactive mix can cause drug redistribution within the system depending on the relative affinity of the drug for the carrier and disintegrant. The drug redistribution that occurs will influence the drug content of the original carrier interactive units and the newly formed disintegrant interactive units. The mixing of these interactive units will occur randomly, and therefore, the particle size differences between the units will influence the degree of interactive unit segregation. Explotab and Starch 1500 were used for further experiments as examples of ternary components possessing high and low drug affinity respectively.

Influence of ternary disintegrant concentration

The homogeneity of mixtures of the 0.25% diazepam-lactose granule 250–425 μm interactive system with Explotab and Starch 1500 125–150 μm in different concentration showed CVs ranging from 0.9 to 6.8% (Table 3). The results indicated that the homogeneity of the ternary mixtures depended on the affinity and concentration of the added disintegrant. The addition of 20% of the low affinity Starch 1500 to the preformed interactive mixture (CV = 1.0%) did not produce a homogenous ternary mixture (CV = 6.8%) while ternary mixes containing 5 and 10% of the high affinity Explotab were of questionable homogeneity. All other mixtures possessed CVs well less than 5%.

The addition of Explotab and Starch 1500 (125–150 μm) in different concentrations to the 0.25% diazepam-lactose granule 250–425 μm caused different degrees of diazepam redistribution (Table 3). The redistribution ratio for the high affinity Explotab remained relatively constant over the concentration range (i.e. 0.877 to 0.916) indicating the establishment of an equilibrium distribution between the lactose and disintegrant carriers. In contrast, the Starch 1500 with its lower affinity for the drug removed little of the diazepam during segregation and the redistribution ratio increased with the concentration of the drug in the solid mixture.

The homogeneity of the ternary systems was consistent with the redistribution behaviour. The presence of disintegrants in the diazepam-lactose interactive mixture produced a complex mixture

TABLE 3

Homogeneity and degree of drug redistribution in mixes of a 0.25% diazepam-lactose interactive system (250–425 μm) with modified Explotab and Starch 1500 (125–150 μm) over a 1–20% concentration range

Disintegrant[a]		1.0%	2.5%	5.0%	10.0%	20.0%
Explotab	CV[b]	1.9	3.3	5.4	4.9	2.7
	R[c]	0.916	0.897	0.877	0.880	0.901
	W[d]	87.1	84.9	83.0	78.2	69.2
Starch 1500	CV	0.9	1.3	2.1	3.2	6.8
	R	0.937	0.961	0.981	0.988	1.111
	W	90.3	87.9	85.3	81.9	72.3

[a]A binary diazepam mix subjected to the same segregation conditions produced a redistribution ratio of 0.945.
[b]Cv is the coefficient of variation of the mix after 30 min mixing.
[c]R is the diazepam redistribution ratio and is the ratio of the diazepam concentration above and below the sieve.
[d]W is the percent of mix by weight remaining on the sieve.

consisting of diazepam-lactose and diazepam-disintegrant interactive units, disintegrant particles, and probably some free diazepam particles. The relative proportion of these components in the random mixture affected the homogeneity of the mixture. For example, the addition of increasing concentrations of Starch 1500 (125–150 μm) to the homogeneous 0.25% diazepam-lactose granule 250–425 μm mixture (CV=1.0%) produced less homogeneous mixtures (Table 3) which could probably be attributed to the difficulty of mixing the diazepam interactive units with increasingly larger amounts of free or at least drug deficient disintegrant of a different particle size. Explotab caused the greatest non-homogeneity at the 5–10% level.

The amount of diazepam redistributed to the high affinity Explotab and the low affinity Starch 1500 can be calculated using the redistribution ratios and the weight distributions and the differences in redistribution behaviour are clearly demonstrated in Fig 1. Added Starch 1500 gives little redistribution of the diazepam over the concentration range studied, i.e. the percent of diazepam is reduced by only 5% over a 20-fold disintegrant increase. Explotab, on the other hand, causes marked diazepam removal, i.e. the addition of 20% disintegrant reduces the drug associated with the lactose carrier to about 65%. The influence is most marked at low disintegrant concentrations. Such redistributions not only affect the homogeneity of the particulate system during mixing but also can influence the potential segregation behaviour of the systems during further processing.

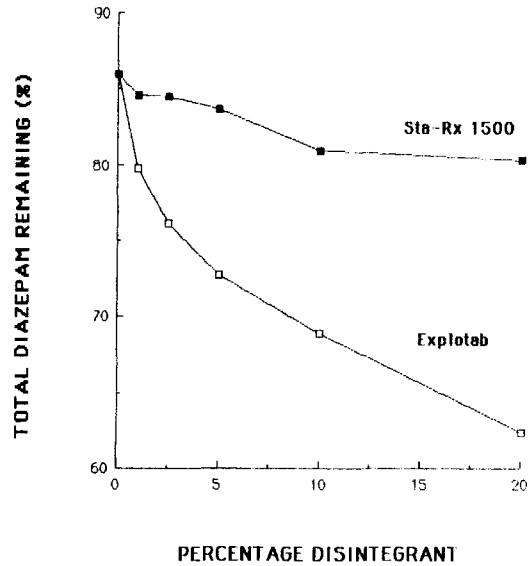

Fig. 1. The influence of disintegrant concentration on the total amount of diazepam remaining associated with the carrier fraction after being subjected to segregation conditions.

Influence of drug concentration

Results shown in Table 4 indicated that for up to 5% diazepam, the homogeneity of all the ternary mixtures was satisfactory as all the CVs were below 5%. The homogeneity of ternary mixtures containing 0.01 and 0.05% diazepam could not be

TABLE 4

Homogeneity and degree of drug redistribution in mixtures of diazepam-lactose 250–425 μm with 5% Explotab and Starch 1500 125–150 μm over the diazepam concentration 0.01–5.0%

Diazepam (%)	Explotab		Starch 1500	
	CV (%)	R^a	CV (%)	R
0.01	b	0.965	b	1.016
0.05	b	0.906	b	1.019
0.10	2.0	0.924	1.8	1.004
0.25	1.1	0.877	2.5	0.981
0.50	1.8	0.930	2.2	0.985
1.00	3.4	0.921	2.4	0.962
2.00	1.8	0.945	2.0	0.975
5.00	1.7	0.938	2.1	0.974

[a]R is the diazepam redistribution ratio and is the ratio of the diazepam concentration above and below the sieve.
[b]Below the detection limits of the analytical method.

observed. A 100 mg sample of those mixtures contained amounts of diazepam outside the limits of detection of the spectrophotometric assay.

The redistribution ratios for diazepam in varying concentrations (0.01–5.00%) in the ternary diazepam-lactose granule 250–425 μm-5% Explotab/Starch 1500 125–150 μm mix were determined (Table 4). Statistical analysis (*F*-test; $p = 0.05$) of these results indicated that there was no significant effect of the diazepam concentration on the stability of the ternary mixtures but a significant difference between the Explotab and Starch 1500 ternary systems was again observed due to the differing diazepam affinities of the two disintegrants. As expected, Explotab which had a high affinity possessed a significantly lower redistribution ratio than Starch 1500 which had a low affinity.

It might be expected that, for a disintegrant which possessed a high affinity for the drug, an increase in drug concentration would result in progressively greater amounts of drug being removed from the carrier until the disintegrant's surface adhesion sites were saturated with drug. Theoretically, if all the drug was removed from the lactose carrier, the saturation of the disintegrant would occur at a drug concentration of 0.4% (calculated from a knowledge of the particle number of each component in the mix and the theoretical number of particles per granule for each material to cause surface saturation). The data have indicated that the high affinity Explotab did not remove all the drug from the lactose carrier at lower drug concentrations but that an equilibrium seemed to exist with the diazepam being distributed between the carrier and disintegrant in the ratio of 9:1.

Influence of carrier particle size

The degree of homogeneity of binary mixtures of 0.25% diazepam with lactose granules after 30 min mixing decreases as the particle size of the lactose carrier increases but is acceptable for all the carrier fractions over the 250 to 1400 μm range (Table 5). A similar homogeneity trend occurred with the addition of 5% Explotab and Starch 1500 (125–150 μm) to this diazepam interactive mixture except that the CVs were generally larger and that unsatisfactory degrees of homogeneity were obtained for the particle size fractions greater than 850 μm. This was probably caused by the wide particle size difference between the disintegrants and the diazepam interactive units enhancing interactive unit segregation. Observation of the mixtures demonstrated that Explotab and Starch 1500 particles separated from the mixture as soon as the mixing process concluded.

TABLE 5

Homogeneity and degree of drug redistribution in mixes of a 0.25% diazepam-lactose with 5% Explotab and Starch 1500 125–150 μm over the lactose carrier particle size range 250–1400 μm

Disintegrant		250–425[a]	425–600	600–850	850–1180	1180–1400
–[b]	CV[c]	1.3	1.4	2.1	4.5	4.8
	R[d]	0.977	0.972	0.922	0.930	0.903
	W[e]	87.5	99.7	99.7	99.6	99.7
Explotab	CV	1.1	1.6	3.5	5.3	6.1
	R	0.987	0.998	0.968	0.976	0.925
	W	78.1	95.5	94.1	95.7	94.6
Starch 1500	CV	2.5	3.4	3.5	5.8	5.3
	R	1.039	1.005	0.987	0.990	0.949
	W	82.6	95.5	95.9	96.2	94.1

[a]Particle size fractions in μm.
[b]Binary diazepam-lactose interactive system.
[c]CV is the coefficient of variation of the mix after 30 min mixing.
[d]*R* is the diazepam redistribution ratio and is the ratio of the diazepam concentration above and below the sieve.
[e]*W* is the percent of mix by weight remaining on the sieve.

The weight distribution of the binary mixes shows that the percent by weight of particles collected for the 250–425 μm fraction was substantially less than all the other higher particle size fractions which remained constant around 99.7%. Such a result might be expected since comminution in the larger size carrier fractions during mixing or segregation would be less likely to reduce the granules below 250 μm. However, any comminution in the 250–425 μm fraction would cause separation of these granules through the 250 μm sieve during the segregation process. The total diazepam lost from the 250–425 μm fraction calculated from the redistribution ratio and the weight distribution was about 32 mg, i.e. 13.5% loss. This loss was due substantially to separation of the comminuted carrier particles and some constituent segregation. However, the loss of diazepam from the larger fractions i.e. 600–1400 μm fractions was small (about 0.8 mg) and was a direct result of constituent segregation. As the particle size of the lactose carrier increased, the redistribution ratio of the diazepam-lactose interactive mixture decreased. Such a decrease is indicative of greater instability of the larger particle size binary mixtures. However, the extent of this trend is small with only between 0.77 and 0.83 mg of diazepam being detached from the carrier over the carrier range 425 to 1400 μm. The binary mixtures were therefore extremely stable during the segregation.

Ternary interactive systems showed the same pattern of redistribution as the diazepam binary interactive system (Table 5). The difference of around 5% in the percent of particles remaining by weight between the binary and ternary mix (Table 5) was consistent with the amount of added disintegrant which would pass through the sieve during segregation. However, additional, unexplained comminution occurred with 250–425 μm fraction when Explotab was mixed. The presence of disintegrant increased the amount of diazepam removed from the lactose carrier, i.e. the weight of diazepam which was lost from the 250–425 μm interactive mixture increased from about 32 mg to 55 mg for Explotab and 42 mg for Starch 1500.

The two disintegrants showed differences in behaviour when added to the 250–425 μm lactose-diazepam interactive mixture. The lower redistribution ratio for this Explotab ternary system (Table 5) was consistent with the disintegrant's greater affinity for the diazepam and probably was due to both constituent segregation and diazepam attachment onto the high affinity Explotab surface. The difference in the behaviour of the two disintegrants was not as obvious in the larger carrier fractions with the amount of redistributed diazepam ranging between 11 and 15 mg for both disintegrants over the particle size range from 425 to 1400 μm.

Conclusions

The addition of a disintegrant to a preformed interactive mixture caused a redistribution of drug between the carrier and the added disintegrant. The degree of redistribution depended on the relative affinity of the drug for the carrier and the disintegrant and was influenced by particle size and concentration of the disintegrants, the drug concentration and the carrier particle size. Such redistributions will affect the homogeneity of the drug during normal powder mixing and, in particular, under conditions of segregation, e.g. handling and transportation of granulations, tabletting and capsule filling operations. While this research has been performed using artificially created size fractions of disintegrants to allow the mechanisms of drug redistribution to be studied, the results have indicated that care should be taken in the design and processing of ternary interactive systems.

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