FACTORS INFLUENCING ON DIAZEPAM HOMOGENEITY IN BINARY INTERACTIVE MIXTURE WITH DIFFERENT CARRIERS

FAKTOR-FAKTOR YANG BERPENGARUH PADA HOMOGENITAS DIAZEPAM DALAM CAMPURAN INTERAKTIF BINER DENGAN BERBAGAI PEMBAWA

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ABSTRACT

Interactive mixing requires an interaction between particles, i.e. interaction of fine particles with the surface of larger particles as the carrier. Two type of forces exist at the particle interface: adhesion and detachment force. The interactive mixing process should depend on carrier particle size, fine particles concentration and affinity of the carrier.

Interactive mixtures were made by using diazepam in different concentration with carrier in different types and particle sizes. The mixing process was done in a cube mixer. The degree of affinity of the carrier surface to diazepam was determined by ultracentrifuge method. The conclusion and recommendation from this study were to use Eudex and lactose-starch granules as the carrier for the future studies. Eudex and lactose-starch granules represent the carrier having high and low affinity for diazepam respectively. Result showed that time needed for a satisfactory degree of homogeneity for the diazepam (0.25%) lactose granule interactive mixtures was dependent on the carrier particle size. The homogeneity of the microcrystallized diazepam lactone granule (250-425 μm) mixture at different diazepam concentration also showed the time dependency. But for Eudex as the carrier there was little effect of diazepam concentration and particle size of Eudex in the mixing time needed for satisfactory degree of mixtures homogeneity.

It can be concluded that the homogeneity of the binary interactive mixture was affected by the affinity, and particle size of the carrier and the concentration of diazepam as well.

Key words: interactive mixture, homogeneity, diazepam

ABSTRAK


Campuran interaktif dibuat dengan menggabungkan diazepam bulat dalam kadar bervariasi dan partikel pembawa dalam berbagai ukuran dan ukuran. Pencampuran dilakukan dalam 'cube mixer'.

Dengan adanya perubahan partikel pembawa terhadap diazepam diuji dengan cara penelitian. Dari hasilnya ditemukan bahwa untuk pembentukan sediaan dapat digunakan Eudex dan granul lactose-amylum, yang masing-masing berturut-turut mewakili

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partikel pembawa benih tanah tinggi dan rendah. Hasil penelitian ini menunjukkan bahwa waktu yang diperlukan untuk menghasilkan campuran interaktif diazepam (0.25%) - granul laktosa tergantung pada ukuran partikel granul pembawa. Homogenitas campuran interaktif diazepam dalam berbagai kadar dengan granul laktosa (256-425 μm) juga memerlukan waktu yang berbeda. Namun untuk Eindex sebagai partikel pembawa, hasil penelitian menunjukkan bahwa kadar diazepam mampu mengurangi partikel pembawa penggunaannya kecil terhadap waktu yang diperlukan untuk tingkat homogenitas campuran.

Data diambil dari bahwa homogenitas campuran interaktif beras dipengaruhi oleh afluensi dan ukuran partikel pembawa saja oleh kadar diazepam.

Kata kunci: campuran interaktif, homogenitas, diazepam.

INTRODUCTION

Interactive mixing requires an interaction between particles, i.e. interaction of fine particles with the surface of larger particles as the carrier. Two types of forces exist at the particle interface: adhesion and detachment force. The homogeneity and stability of the pharmaceutical interaction mixtures have been studied (Stewart, 1984; Thri and Stephenson, 1982; Soehnagl and Stewart, 1985; Schmutz and Rubenendorfer, 1994). Interactive mixing of a drug offers potential applications in the production of low dose tablets or capsules. Diazepam is one of the low dose drugs. The factors affecting on diazepam homogeneity of the interaction mixtures has not been studied in detail, so that the such factors are presented.

METHODOLOGY

Materials and methods. Micronized diazepam (Alphapharm, grade B P. d₅₀ = 3.1 μm) was used as the drug model. The carriers were lactose-starch granules (2.1% prepared by wet granulation using starch paste as the binder), Avicel, Microtoll and Eindex. The carrier fractions were obtained by sieving classification using a Pascal sieve shaker containing Eindex screens.

Ultracentrifuge Method (Kuhlman, 1986). The carrier was hand compressed without lubricant using Mazerity E. 2 single punch tablet machine and 5.5 mm concave punches. These tablets of average weight approximately 60 mg and hardness of more than 15 kg (Eirweka tablet hardness tester, model TWT) were mixed with 1% diazepam in the bottle until all diazepam had adhered on the tablet surface to produce the interactive system. A specially designed centrifuge cell was made from aluminium. It consisted of the sample and collection compartments, split by a rotatable screen of intermediate size between carrier and drug particle. A sample of interactive mix (a tablet of carrier containing 1% diazepam) was placed in the sample compartment, the screen was then inserted over it and separated diazepam powder, collected in the collection compartment during centrifuging with 2000, 5000, 10,000, 15,000, and 19,000 rpm for 30 seconds of each speed. The centrifuge cell was held in position within the centrifuge rotor by the cradle so that the screen was normal to axis of rotation. During centrifuging the screen allowed the separation of diazepam and by retaining the mixture in the sample compartment but permitted detached diazepam particles to pass into the collection compartment. The distance between axis of rotation and screen was 6.7 cm. The amount of collected diazepam powder was analyzed spectrophotometrically.

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Mixing Method. Powder mixing of larger quantities was performed using an Fruehauf Cube mixer (20 rpm, load 100-500 g) and smaller powder loads (load 10-25 g) were mixed using a glass bottle attached to the side of the cube mixer (20 rpm).

Homogeneity Evaluation. Twenty 100 mg samples were removed randomly for assay of the drug content. The samples were removed using a sample thief to minimize any disturbance to the mix. The homogeneity was expressed by the coefficient of variation. The homogeneity standard for satisfactory mixing was the coefficient of variation necessary to comply with a pharmacopoeial or manufacturing standard (Stewart, 1981). For example, for 95% of samples falling within ±10% of the mean, the coefficient of variation is 5%.

RESULTS AND DISCUSSION

Affinity Studies

Several carriers were used to determine the degree of interaction or affinity between diazepam and the carrier surface using an ultracentrifuge method. Ideally, the affinity showed be determined between diazepam and carrier granules. However, granules of both lactose and Eudex were suspended during centrifugation. In this study materials were preliminary compacted into a small tablet with high hardness (60 mg, >15 kg), so that the tablet did not break up during centrifugation. The cohesion between 1% of diazepam and tablet surface was determined.

From the adhesion measurement data, the adhesion profile shown in Fig. 1 were obtained when the percentage of diazepam remaining was plotted against the speed of rotation (Kuharich, 1985). The plot showed the adhesion tendency of the 1% diazepam-carrier Eudex, lactose-starch granules, Avicol and Mavast, interactive mix. Adhesion profiles showed: 1. Diazepam was relatively strongly adhered to the carrier surface. 2. There was a difference in behavior between the carriers.

![Fig 1: Adhesion profiles of 1% diazepam-carrier interactive system: A: Avicol, B: Lactose granule, C: Mavast, D: Eudex](image)

The adhesion data has been reported to show characteristic profiles which were log normal distribution functions. Linearization of the adhesion profiles may be achieved using logarithmic-probability coordinates by plotting values of logarithms of square of rotor speed (SR) on abscissa against the percentage of drug retained on a probability scale. Kulvanich (1986) stated that such linear plots allowed the determination of the median speed of detachment, $S_{50}$ (the speed at which 50% of drug was detached) and the standard deviation of adhesion distribution. The standard deviation of adhesion was calculated from the relation, standard deviation = $S_{25} - S_{75}$, where $S_{50}$ is the speed at which 10% of drug was retained on carriers. The parameter $S_{50}$ and standard deviation can be used for evaluating the adhesion tendency of drug particles to the carriers. The parameter $S_{50}$ characterizes the adhesion of the drug particles, the greater the $S_{50}$ value, the higher the degree of interaction between drug particles and carriers. The standard deviation value measures the scatter of minimum and maximum of the relative centrifugal force corresponding to the rotor speeds required to detach drug particles.

![Diagram](image)

**Fig 2**: Logarithmic-probability plots of % retained diisopropylcarbamine against square of centrifugation speed for the adhesion profiles of diisopropylcarbamine-carrier in Fig.1

- □ Avicel
- ▼ Marisolv
- ■ Lactose grade B
- ▲ Emedex

Fig 2 indicated that logarithmic-probability plots of drug retaining against square of centrifugation speed for the adhesion profiles of diisopropylcarbamine-carrier in Fig.1 showed poor linearity. Because of the strong adhesion between drug and carrier, $S_{50}$ and $S_{75}$ could not be used since diisopropylcarbamine on the different carriers at the maximum speed used, was above 50%. In addition, estimation of $S_{50}$ and $S_{75}$ would be unreliable due to the poor linearity. All observed carriers had strong adhesion or great affinity characteristics for diisopropylcarbamine. To compare the affinity of the carriers for diisopropylcarbamine, $S_{50}$ (the speed at which 50% of diisopropylcarbamine was retained on carriers) was used. The adhesion profiles (Fig.1) indicated that Emedex had the strongest adhesion.
or greater affinity for diazepam, followed by lactose-starch granules. Avicel and Mannitol had the least adhesion or affinity ($S_{ad}$ for Emdex, lactose granule, Avicel and Mannitol was 21000, 15000, 13000 and 7000 rpm respectively).

The conclusion and recommendation from this study were to use Emdex and lactose-starch granules as the carriers for further studies. Both of these carriers were available in wide tablet particle size ranges and had different affinity for diazepam. Emdex and lactose granules represent the carriers having high and low affinity for diazepam respectively.

**Binary Mixtures**

Binary interactive mixtures were obtained by mixing 0.25% micronized diazepam with lactose granule in 106-250, 250-425, 425-620, 600-850, 850-1180 and 1180-1400 µm diazepam in 0 10%, 0 25%, 0 50% and 5 0% with lactose granule 250-425 µm, 0 25% diazepam with Emdex in 106-250 and 250-425 µm, 2 0% diazepam with Emdex in 106-250 and 250-425 µm.

The coefficient of variations (CV) was chosen in this study to describe the degree of homogeneity. The homogeneity standard was the coefficient of variation necessary to comply with pharmacopoeial or manufacturing standard (Stewart, 1981); the CV of less than 5% was considered satisfactory, i.e. 95% of samples fell within ±10% of mean.

<table>
<thead>
<tr>
<th>Missing time (minutes)</th>
<th>0.25% Diazepam-lactose granule</th>
<th>106-250</th>
<th>250-425</th>
<th>425-620</th>
<th>600-850</th>
<th>850-1180</th>
<th>1180-1400</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>x</td>
<td>145.4</td>
<td>121.1</td>
<td>111.9</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>x</td>
<td>2.5</td>
<td>31.3</td>
<td>7.7</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>175.2</td>
<td>2.5</td>
<td>3.7</td>
<td>71.1</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>6.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>6.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>4.5</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

$x = ^{not} observed$; the separated diazepam aggregation was clearly seen in the mixture.

The time needed for a satisfactory degree of homogeneity for the diazepam (0.25%)-lactose granule interactive mixtures was dependent on the carrier particle size (Table I). The homogeneity of the micronized diazepam-lactose granule (250-425 µm) mixture at different diazepam concentration also showed the time dependency (Table II).

The kinetics of interactive mixing process probably involve two steps: Deaggregation of the micronized aggregates which will be formed in the cohesive micronized drug powder, and adhesion of the deaggregated particles onto the surface of the carrier.

The relative importance of these two processes should depend on both the particle size and drug concentration. The rate of deaggregation will be increased by the presence of large

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carrier particles which will tend to "ball mill" the aggregates through the impact force generated during mixing. The rate of mixing would be expected to increase as the drug concentration decreases given the degree of aggregation will also depend on the drug concentration with the larger concentration producing more and larger aggregates that other factors remain constant. The rate of drug adhesion will be dependent on the number of adsorption sites on the surface, smaller carrier particles should therefore experience a greater rate of adhesion.

The rate of mixing in any particles system will be dependent on the balance of these two effects and the data containing Table I and II is well explained by consideration of disaggregation and adhesion processes.

Table II: Mixing profile for micronized diaspate in different concentrations-lactose granule 250-425 µm

<table>
<thead>
<tr>
<th>Mixing time (minutes)</th>
<th>Diazepam-lactose granule 250-425 µm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.10 %</td>
</tr>
<tr>
<td>5</td>
<td>43.6</td>
</tr>
<tr>
<td>10</td>
<td>1.8</td>
</tr>
<tr>
<td>20</td>
<td>3.3</td>
</tr>
</tbody>
</table>

x = not observed; the separated diaspate aggregation was clearly seen in the mixture

Table III: Mixing profile for interactive mixture of micronized diaspate in different concentrations and Eudex in different particle size

<table>
<thead>
<tr>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixing time (minutes)</td>
</tr>
<tr>
<td>Diazepam- Eudex 106-250 µm</td>
</tr>
<tr>
<td>0.25 %</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>60</td>
</tr>
</tbody>
</table>

x = not observed; the pyramidal diaspate aggregation was clearly seen in the mixture

Table III shows that the binary interaction mixtures containing diaspate in different concentrations and Eudex in different particle size reached their satisfactory homogeneity after 60 minutes mixing, there was little effect of the drug concentration and particle size of the carrier on
the mixing time needed for a satisfactory degree of homogeneity. Table I, II and III show the poor initial homogeneity of the mixture which improved with time. These results reflect the effect of the initial distribution of diazepam in the binary interactive mixture. The cause of the poor homogeneity may be the difficulty in the random mixing of diazepam-carrier adhesion units and small portion of the diazepam aggregates.

CONCLUSION
The homogeneity of the binary interactive mixture of diazepam-carrier was affected by the affinity and particle size of the carrier and also by the concentration diazepam.

REFERENCES


different carriers after 90