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Dissolution from ordered mixtures: The effect of stirring rate and particle characteristics on the dissolution rate.

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Abstract

Different particle size fractions of three carriers were used to prepare ordered mixtures of frusemide. The dissolution of these mixtures were compared with a frusemide suspension and pure frusemide agglomerates by the USP XXI paddle method at three rotational speeds.

The dissolution of mixtures containing a highly soluble carrier (sodium chloride) were comparable to the suspension depending on the particle size of the carrier. Insoluble carriers (dicalciumphosphatedihydrate and microcrystalline cellulose) increased the dissolution, but the enhancement depended on the rotational speed, the particle size and the density of the carrier.

Introduction

Ordered mixtures are produced through dry mixing, whereby agglomerated drug particles are separated and distributed over the surface of the carrier material [1]. Adhesion results either from inherent surface forces of smaller particles or from surface tension effects of adsorbed moisture [2]. Hersey [1] reported that the cohesive properties of powders and other surface phenomena usually develops with increasing fineness resulting in an ordered rather than a random mixing operation.

Ordered mixtures may be used to increase the dissolution rates of sparingly soluble fine-particulate drugs, because a large contact surface area is exposed to the dissolution medium [3/4/5]. According to Westerberg et al. [4]

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a requirement for fast dissolution from an ordered mixture, seems to be the rapid dissolution of carrier particles, delivering a fine particulate suspension of drug particles. They found that insoluble carriers gave a limited increase in dissolution rate because of a increased influence of diffusional transport and a decrease in the surface area participating in dissolution. The decreasing surface area could be attributed to the distribution of the carrier particles in the USP XXI paddle dissolution apparatus.

The aim of this study was to determine the effect of carrier particle distribution, in the dissolution medium, on the dissolution of ordered mixtures. The dissolution of frusemide ordered mixtures, with soluble and insoluble carriers, were determined, at three rotational speeds, with the USP XXI paddle method. The effect of the particle size of the carrier was also investigated. Results were compared with the dissolution of a frusemide suspension and frusemide agglomerates.

Materials and methods

Materials

Frusemide (supplied by Propan, Johannesburg) was used as a substance representing a fine particulate and sparingly soluble drug. It had a mean particle size of 14.6 μm and a maximum size equal to 39.4 μm (determined with a Coulter Counter). Because of its cohesive nature, frusemide is strongly agglomerated. The agglomerates in the sieve fraction 500-700 μm were used in the mixing. Three carrier materials, sodium chloride (BDH Chemicals), dicalciumphosphatedihydrate (Emcompress, E. Mendell, U.S.A.) and microcrystalline cellulose (Avicel PH 102, FMC) were milled (Retsch type ZMI, Wes-Germany) and then granulated (Erweka type F.G.S., Wes-Germany) with a 10 % gelatin solution. The granules were dried for 24h at 60 °C and then fractionated by sieving. The fractions 50-80, 120-180, 210-250 and 300-350 μm were used. Sodium chloride represents a highly soluble material with a high density. Emcompress and Avicel were chosen because of their low water solubility. Emcompress represents a high and Avicel a low density material.

Mixing

Mixtures of the different sieve fractions, were mixed in 340 ml glass bottles (70 mm diameter and 125 mm length), in a Turbula mixer (model 2P) at 90 rpm. One mixture (50 ml carrier and 50 mg frusemide agglomerates) was prepared for each of the different sieve fractions of each carrier. To ensure total deagglomeration mixing was performed for 120-240 min. After mixing was completed the mixtures were left for 24h to reach equilibrium. To test that no agglomerates were present each mixture was sieved using the sieves that formed the borders of the carrier fraction. Each mixture was capsulated, in total, in no. 2 size hard gelatin capsules.

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The Frusemide Content of the Capsules

The frusemide content of twenty capsules of each mixture were determined by dissolving the content of each capsule in 100 ml 0.1 M sodium hydroxide, filtering the solution (2 μm microporous filter) and measuring the UV absorbance at 271 nm using a spectrophotometer (Hitachi, model 100-20). The mean content of frusemide of each mixture, as a percentage of the theoretical amount in each capsule, was calculated.

Dissolution studies

The dissolution test was performed according to the USP XXI, paddle method. Three rotational speeds, 25, 50 and 150 rpm were used and the temperature was kept constant at 37 °C. The ordered mixtures, a frusemide suspension in 0.1 M hydrochloric acid and pure frusemide as agglomerates were tested. The dissolution medium was 500 ml acetate buffer pH 4.6. Samples were taken after 1, 2, 4, 8, 16, 32 and 64 min from the dissolution medium with a 10 ml pipet through a 2 μm microporous filter. An equivalent amount of buffer (at 37 °C) was added to the dissolution medium to replace the amount taken out. After the last sample was taken the dissolution flask was removed and placed in an ultrasonic bath for 15 min after which another sample was taken. This was done to determine the total amount of frusemide present in each capsule. The concentration of frusemide in each sample was determined by measuring the UV absorbance at 271 nm. Results presented are mean values of three determinations.

Calculations and Statistical interpretations

To obtain a single factor to compare the dissolution profiles, the area under the curve (AUC) was calculated. The equation that best described each dissolution profile was found by the method of least squares. The area under the dissolution curve was calculated integrating the equation, up to 32 minutes, that best described the profile.

Mean values of the content uniformity and the AUC for each mixture were compared with control groups for significant differences at a 95 % confidence level, using Dunnett's test for the comparison with a single control group. Calculations were done with a BMDP7D program (BMDP Statistical Software, University of California).

Results and Discussion

The mean values for the content uniformity of the ordered mixtures are presented in Table 1. According to the statistical analysis there were no significant difference in the frusemide content of the mixtures, except for the Avicel 50-80 μm mixture. This mixture had a C.V. value of 16.54 % com-

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TABLE 1

Properties of frusemide capsules containing ordered mixtures of frusemide with different carriers after mixing in a Turbula mixer at 90 rpm for different mixing times.

Carrier	Mean Particle Size Carrier (μm)	Mixing Time (min)	Frusemide Content (%)	Content Uniformity C.V.(%)
Sodium Chloride	65	120	100.65	5.16
	160	120	98.75	2.33
	230	120	99.61	1.51
	325	120	99.31	1.19
Emcompress	65	180	97.62	4.11
	160	180	97.10	3.99
	230	120	99.95	0.48
	325	120	96.40	2.86
Avicel	65	240	95.34	16.54
	160	240	95.48	7.92
	230	240	98.31	2.66
	325	240	98.80	1.34

pared to the mean value of 3.05 % for the other mixtures. These results in combination with the fact that no frusemide agglomerates were present in the mixtures proved that ordered mixtures were formed.

For each dissolution profile the area under the curve (AUC) was calculated. Mean values are presented in Table 2. Figure 1 shows the difference in the ratio of the area under the dissolution curve of the mixtures (AUC(x)) to the suspension (AUC(y)) for the 300-350 μm mixtures at the different rotational speeds.

The AUC's of all the mixtures were greater than that for the frusemide agglomerates. Only the AUC's for the sodium chloride, 300-350 μm mixture (25 rpm), 50-80 and 300-350 μm mixtures (50 rpm) and 50-80, 210-250 and 300-350 μm mixtures (150 rpm) showed no significant difference from the suspension.

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TABLE 2

Mean values of the area under the dissolution curve (AUC, %min) of the ordered mixtures, the suspension and frusemide agglomerates according to the USP XXI paddle method at three rotational speeds.

	Mean Particle Size Carrier (μm)	Rotational Speed (rpm) 25 AUC	C.V.%	50 AUC	C.V.%	150 AUC	C.V.%
Sodium chloride	65	2781	4.05	2973	1.30	3117	1.21
	160	2885	2.20	2946	0.67	2997	0.59
	230	2853	1.95	2883	4.69	3110	1.35
	325	2973	1.51	3127	0.46	3130	1.19
Emcompress	65	1517	8.62	1487	7.34	2797	0.38
	160	1548	6.01	1589	7.09	2782	1.02
	230	1616	3.44	2416	2.05	2794	0.73
	325	1723	2.01	2528	2.49	2803	0.15
Avicel	65	692	5.50	1118	8.33	2829	0.62
	160	1412	6.90	2108	0.51	2901	0.43
	230	1443	6.48	2929	1.28	2937	3.82
	325	1665	5.08	2864	2.54	2946	0.67
Suspension		3072	1.71	3133	2.86	3192	1.82
Agglomerates				491	8.23	762	11.76

Comparison of the AUC's for the Avicel and Emcompress, except for the Avicel 50-80 μm mixture, showed significant differences at 25 rpm. However these AUC's were significantly lower than that of the sodium chloride mixtures and the suspension. At 50 rpm the AUC's for the different Avicel mixtures (except the 50-80 μm mixture) were significantly higher than the equivalent Emcompress mixtures, but for both carriers the larger particles had higher AUC's than the smaller ones. At 150 rpm the AUC's of all the Avicel and Emcompress mixtures and the sodium chloride 120-180 and 210-250 μm mixtures showed no significant difference. These AUC's were however significantly lower than the AUC's of the other sodium chloride mixtures and the suspension.

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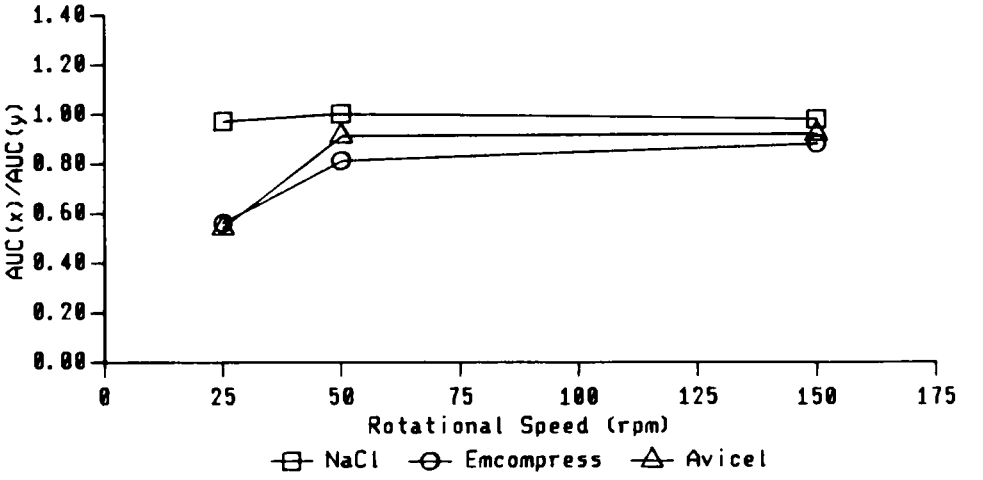

FIGURE 1

The effect of increasing rotational speed on the ratio AUC(x)/AUC(y) for the different 300-350 μm mixtures.

The best dissolution was obtained with the mixture containing the large highly soluble sodium chloride particles (see figure 1). The dissolution of this mixture was independent of the rotational speed. At 25 rpm the action of the paddle is not sufficient enough to distribute the insoluble carrier particles and resulted in the accumulation of the particles on the bottom of the dissolution flask. Many frusemide particles were therefore never in contact with the dissolution medium. The difference in the dissolution rates of the mixtures containing large and small carrier particles, at 50 rpm, was due to the fact that there were fewer large particles per capsule to be distributed. These large particles accumulated loosely on the bottom of dissolution flask, enabling the paddle to circulate them. Avicel was easier dispersed than Emcompress because it has a lower density. The uncharacteristic dissolution behaviour of the 50-80 μm Avicel mixture could be contributed to the fact that a poor ordered mixture formed.

Ordered mixing improved the dissolution of frusemide. This improvement can be attributed to an increased surface area of frusemide in contact with the dissolution medium. Best dissolution was found when the carrier particles were distributed throughout the dissolution medium. The better dissolution rates of the sodium chloride mixtures can be attributed to the high solubility of sodium chloride in the dissolution medium thereby dispersing the frusemide particles, forming a fine particulate suspension [4].

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Conclusions

The increased dissolution of ordered mixtures of frusemide corresponds with reports in literature for other poorly soluble and poorly wettable drugs. The results of this study however led to the following conclusions:

- The dissolution of ordered mixtures of frusemide is independent of the rotational speed, and comparable to a suspension, if a highly soluble carrier with large particles is used.
- If the insoluble carrier particles are dispersed throughout the dissolution medium the dissolution of an ordered mixture is independent of the particle size of the carrier.
- The dissolution of mixtures containing insoluble carriers depend on the density and the particle size of the carrier, at low rotational speeds.

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