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Incorporation and distribution of a low dose drug in granules

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Summary

The mixing technique of a low dose active ingredient with the bulk material is very important in pharmaceutical preparations. In the present work, manual pregranulation mixing and pregranulation mixing with a double-cone mixer were carried out. The efficiency of pregranulation mixing followed by fluidised bed granulation was compared with the technique of drug distribution through the granulating liquid. Drug was dissolved with different volumes of PVP solution and water for distribution in bulk material. The mixing of the drug particles with the bulk material by both pregranulation manual mixing and using a double-cone mixer did not achieve satisfactory drug distribution. Mixing efficiency was found to improve with an increase in the proportion of the granulating liquid used to distribute the drug It was also found that an optimum atomizing pressure is necessary for promoting uniform mixing

Introduction

In the preparation of solid dosage forms, there is always the need to mix two or more constituents to produce a homogeneous mixture. The mixing technique is most important but is difficult to perform for microdose preparations where the active ingredient represents less than 5% of the total mixture. From the standpoint of drug dissolution and bioavailability, the active ingredient should be as uniformly distributed in the dosage form as possible and should show uniform content even upon further subdivision. Homogeneous mixing between particles of different sizes and shapes is difficult (Hunter and Ganderton, 1973). This problem is exacerbated when one component is a low dose drug. In a fluidised bed system, mixing and granulating occur simultaneously. Each particle of the bulk material has an equal opportunity to come in contact with the fine droplets of drug solution which is sprayed onto the granulation. Post-mixing granulation is carried out to prevent segregation of mixer components.

This paper presents the findings on the distribution of a drug of low dose in granules which were prepared with different mixing techniques for incorporating the drug.

Materials and Methods

Lactose (Pharmatose 200M, DMV, The Netherlands) and chlorpheniramine maleate

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(mean size, 65.1 ± 7.2 μm; B.P.) were used as supplied. An aqueous solution of 5% w/v of polyvinylpyrrolidone (PVP, Plasdone K-90, GAF, U.S.A.) and distilled water were used as the granulating liquids.

Drug distribution in granules

Incorporation of a low dose drug, chlorpheniramine maleate 1% (w/w) in lactose (400 g), was attempted via three methods: manual pregranulation mixing, pregranulation mixing using a double-cone mixer and spraying of an aqueous solution of drug.

Manual pregranulation mixing

The manual pregranulation mixing method involved the mixing of the drug initially with an equal portion of lactose using a spatula. The mixture was mixed further with an equivalent amount of lactose. The process was repeated until all the lactose was mixed with the drug. After completion of this mixing process, the mixture was transferred to a fluidised bed chamber (Niro Aeromatic, Strea 1, Switzerland) and granulation was carried out using 90 ml of 5% PVP solution.

Pregranulation mixing in double-cone mixer

In the pregranulation mixing using a double-cone mixer (Train, 1960) a weighed amount of drug and lactose were introduced into the mixer. The mixer was spun at 15 rpm for 30 min. After completion of mixing process, the drug-lactose mixture was granulated in a fluidised bed granulator using 90 ml of 5% PVP solution.

Spraying of an aqueous solution of drug

The amount of drug to be distributed was dissolved in 30 ml water and sprayed onto the lactose in the fluidised bed granulator prior to the incorporation of 90 ml of 5% PVP solution. In further experiments, the drug was dissolved in 20, 40, 50, 60, 70 and 90 ml of 5% PVP solution and sprayed as in the above. Completion of granulation was carried out with the balance of PVP solution, if any, to a total volume of 90 ml of 5% PVP solution for granulation.

Fluidised bed granulation

The rate of spray of the granulating fluid was 14 ml/min and a total of 90 ml of 5% PVP solution was used. The inlet air volume was maintained about 75 m^3/h and the atomizing pressure was 1.2 bar with nozzle height set at 39 cm above the base plate (Wan and Lim, 1988, 1991). In the studies on the influence of atomizing pressures, the pressures used were 0.5, 1, 2 and 3 bars.

Size analysis

A nest of sieves of aperture sizes 106, 180, 250, 355, 500, 710, 1000, 1400 and 2800 μm (Endecotts Test Sieves, U.K.) were used for size analysis and separation of the granules in different size fractions. The sieves were vibrated (Endecotts Sieve Shaker, EVS 1, U.K.) at an amplitude of 1 mm for 15 min.

Drug content of granules

The drug content of the granules was determined by dissolving an accurately weighed amount of granules, 20–40 mg, from random samples in 10 ml of distilled water and the UV absorbance determined at a wavelength of 261 nm (Perkin-Elmer, 550, U.S.A.). The mean drug content for each batch was evaluated using 25 samples. Upon separation of the granules into various size fractions, the drug content determinations were also carried for size fractions 106–180, 500–710, 1000–1400 μm, representing small, medium and large granules.

Results and Discussion

The various methods of distribution of a low dose drug in the fluidised bed granulator were studied using chlorpheniramine maleate-lactose formulations with PVP as the granulating liquid. The uniformity of drug distribution in granules is best studied using a large number of randomly picked very small samples and determining the drug content in each sample. The standard error of the drug content was calculated. The deviation of the drug content for a size fraction from the mean drug content of that batch, and the standard error of the drug content of the samples can

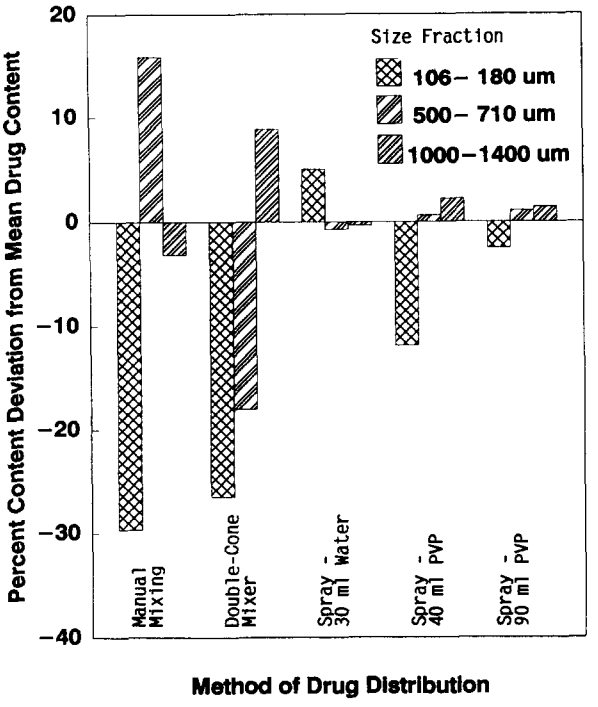

Fig 1. Percent deviation of drug content for various granule fractions produced using different methods of drug distribution.

determine the uniformity in the drug distribution between different size fractions and between different methods of drug incorporation.

In the case of mixing manually and in the double-cone mixer before being granulated in the fluidised bed granulator, the percent deviations of drug content for all size fractions of granules from the overall mean drug content of the batch were very high (Fig. 1). Several factors could be responsible for this high deviation. Shear forces are necessary to produce relative movement of the particles and these must be applied to a particular system by some external means, so that by interparticulate transmission they may act within the bed. Inadequate forces permit the presence of dead zones within a system or allow aggregates of particles to move round as compound entities, within which no relative movement or particle exchange takes place. If the force is very high, the particles would adhere to the wall of the double-cone mixer without any relative movement of particles. In manual mixing the shear force applied was substantially less than that required for uniform mixing. Greater size of drug particles and very large difference in respect of the proportion of drug and bulking material were not favourable for uniform mixing when the drug was mixed in a double-cone mixer and in manual mixing.

Electrostatic charges and Van der Waals forces present on the surface of the particles effect adhesion. These forces cause groups of particles to be held together as aggregates. It becomes consequently difficult to disperse the aggregates evenly. In order to improve drug distribution, attempts were made to distribute the drug by spraying.

In the fluidised bed, when the drug was distributed by dissolving and spraying with 40 ml of 5% PVP solution and 90 ml of 5% PVP solution or 30 ml water, a higher percent deviation from the overall mean drug content was found for the smaller granules as compared to the medium and larger granules (Fig. 1). The smaller granules or fines were the remnants of lactose particles that had not undergone granulation or were particles broken down from the agglomerates formed. A large fraction of the fines was the result of lactose particles adhering to the filter bag during the granulation process. These fines were less involved in the granulation and consequently had a lower drug content when drug was distributed with 40 and 90 ml of PVP solution. A positive deviation was obtained when the drug was incorporated using 30 ml water. When water was used to distribute the drug, it is likely that the lower viscosity of the spray solution produced finer droplets, resulting in a higher propensity to spray drying in the fluidised bed. The small extent of spray drying during the process formed fine drug particles which contributed a higher drug content to the 106–180 μm granule fraction.

The proportion of the granulating liquid used to dissolve the drug also affected the uniformity of the drug distribution in the granules. Increasing the proportion of granulating liquid from 40 to 90 ml of 5% PVP used to disperse the drug decreased the percent deviation from overall mean drug content for the small granules by

9.39% (Fig. 1). Nevertheless, the granules in the size fraction of 106–180 μm form less than 5% of the total granules in all batches (Fig. 2).

Studies were carried out to investigate the effect of dissolving the drug in varying proportions of PVP solution. The standard error in drug content was calculated as the index of uniformity of the drug distribution in the granules. Standard error was comparatively high when the drug was sprayed with 20 ml of 5% PVP solution (Fig. 3). The standard error was reduced significantly when 40 ml of PVP solution was used. Further increase of this volume resulted in a further decrease of the standard error, albeit to a lesser extent. Increasing the proportion of granulating liquid used to dissolve the drug enhanced the distribution of drug in the granules. In all cases, a total of 90 ml of 5% PVP solution was used for mixing and completion of granulation.

The homogeneity of the powders blended by fluidising and the uniformity of heat transfer that takes place in the bed depend on the behaviour

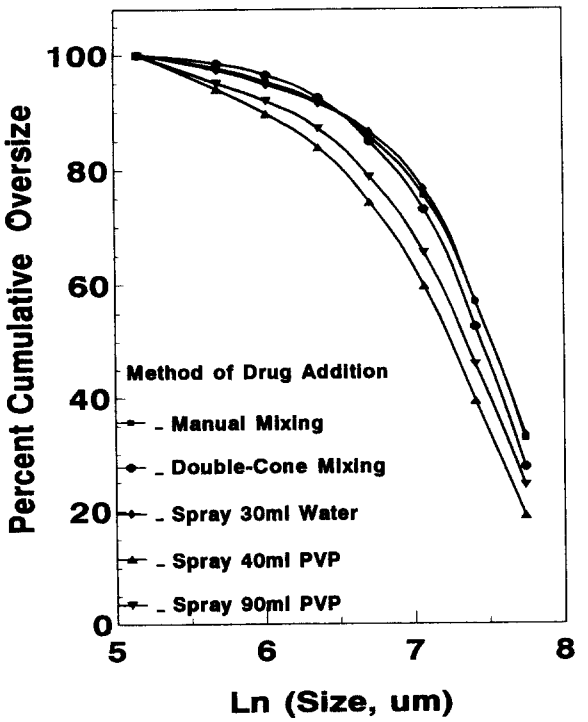

Fig 2 Size analysis of granules following different techniques of drug addition

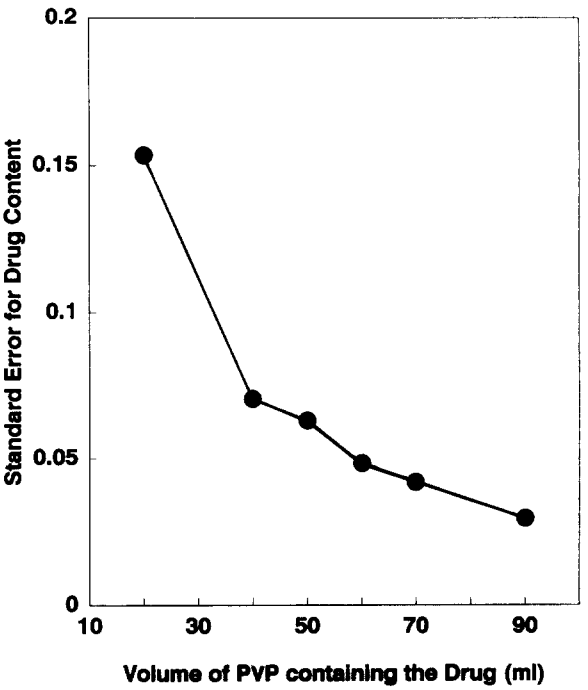

Fig. 3 Variation of standard error for drug content with different volumes of 5% PVP solution used to distribute the drug.

of the particles when fluidised. Each particle should be suspended individually in the gas to facilitate contact with the droplets of liquid and with the incoming hot air which effects drying. Factors such as size of the droplets, the droplet life-time and time required for drying the droplets deposited onto the particle surface play an important role in achieving uniform mixing. These factors are dependent on the atomizing pressure used in fluidised bed granulator. The effect of atomizing pressure on the uniformity of mixing was investigated when the drug was dissolved in 30 ml of water for mixing. A low atomizing pressure (0.5 bar) produced coarse droplets. The number of droplets produced was numerically less and was insufficient for the distribution of the drug within the large amount of bulk material. This caused an uneven mixing of drug with lactose, thereby resulting in a higher standard error for the drug content in the granules (Fig. 4). When the atomizing pressure was increased to 1 bar, finer droplets were formed. The droplets

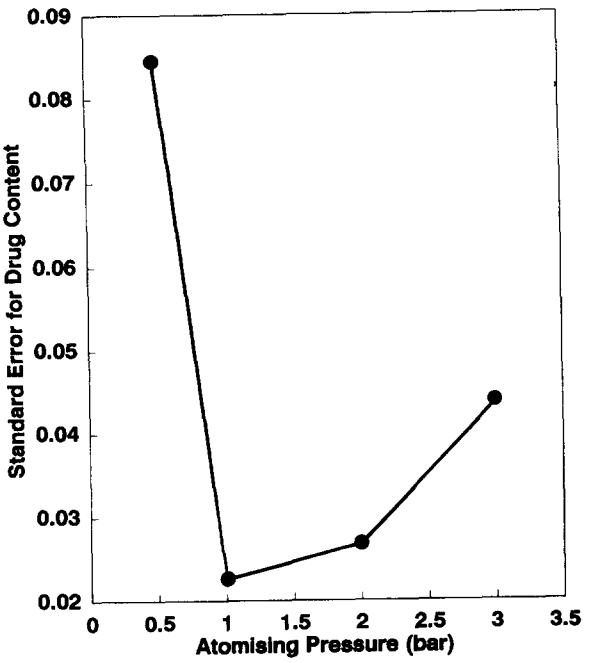

Fig. 4. Effect of mixing in a fluidised bed granulator with different atomising pressures.

were more numerous and were adequate for uniform mixing with a large amount of bulk material. This resulted in better mixing and the standard error for drug content in the granules was very low (Fig. 4). Further increase in the atomizing pressure to 2 and 3 bar produced very fine droplets. However, the higher atomizing air flow rate caused core channelling at the centre of the bed. This reduced the efficiency of the fluidised bed. In addition, the very fine droplets had a greater tendency to spray drying on contact with the hot incoming air and causing less even distribution of drug as indicated by the higher standard error.

The findings of this study indicate that the distribution of a low dose drug in a fluidised bed granulation is best achieved through dissolving the drug in the granulating liquid. The mixing of the drug particles with the bulk material by both pregranulation manual mixing and by using a double-cone mixer did not achieve satisfactory drug distribution. Mixing efficiency is found to increase with an increase in the proportion of the granulating liquid used to dissolve the drug. It was also found that an optimum atomizing pressure is necessary for promoting uniform mixing.

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