ELSEVIER

International Journal of Pharmaceutics 141 (1996) 161–170

international journal of pharmaceutics

Effect of polyvinylpyrrolidone solutions containing dissolved drug on characteristics of lactose fluidized bed granules

Lucy S.C. Wan*, Paul W.S. Heng, B.L. Ling

Department of Pharmacy, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260, Japan

Received 29 April 1996; accepted 6 June 1996

Abstract

The use of different grades of polyvinylpyrrolidone (PVP) in solutions containing dissolved drug with lactose as feed material for fluidized bed granulation were studied. The action of PVP K25, K29–32 and K90 influenced the characteristics, such as mass median diameter, span, wt.% < 250 μm and crushing strength of the granules. This was associated with the volume and concentration of PVP solution used. Increasing the volume of binder solution subjected the feed material to a prolonged granulation process and increased the total quantum of binding effect. The feed material responded through the formation of larger granules. The span and wt.% < 250 μm decreased. This was attributed to secondary agglomeration, layering effect being the prominent process. The crushing strength values were higher for larger volume and higher concentration of binder used. This is due to more binder being deposited on the granules, which when dried would manifest as solid bonds, giving tenacity to the structural framework of the granule. The viscosities of PVP K25 and K29–32 solutions were similar to corresponding solutions with dissolved drug. As such, characteristics of granules with PVP K25 were similar to those with PVP K29–32. In the case of PVP K90, this binder was able to confer strong bonds to the granules and this enabled them to better withstand the effects of attritive forces generated during granulation. The opportunity for size growth was greatly enhanced. As a result, the mass median diameter was higher, the span value and percentage weight < 250 μm relatively lower with respect to corresponding batches produced with PVP K25 and PVP K29–32.

Keywords: Polyvinylpyrrolidone; Dissolved drug; Fluidized bed granules; Mass median diameter; Span; Crushing strength

* Corresponding author.

PII S0378-5173(96)04633-9

1. Introduction

The mechanisms of granule formation and growth are vital in determining the outcome of the granulation process. The final properties of the granules such as size and shape of granules are dependent to a large extent on the mechanisms involved, the interplay of forces in the conversion of the starting material to the formation of a desirable collection of granules. Binder solutions can bring about nucleation, layering as well as coalescence between two colliding particles (Schwartz, 1988). Nucleation occurs when there is sufficient liquid to establish bridges. Layering process occurs between a large particle and many smaller particles. Growth by coalescence presupposes the presence of free surface liquid which can establish liquid bonding (Kristensen, 1988). Fluid bed technology allows efficient mixing, agglomeration and drying, and these processes can be performed in one operation in the same chamber (Schaefer, 1988). Advantages include optimization of processing parameters, reproducibility and with products satisfactory characteristics such as mechanical strength, disintegration and dissolution properties (Zenz et al., 1984; Olsen and Mehta, 1985). Many factors affect fluidized bed granulation (Rankell et al., 1964; Mehta et al., 1977; Aulton and Banks, 1978; Lipps and Sakr, 1994).

Process and product variables, including binder solution and liquid flow rate on fluidized bed granule size and size distribution have been studied (Schaefer and Worts, 1977a,b; Schaefer and Worts, 1978a,b,c). Investigations relating to the quantity, concentration and viscosity of the granulating liquid on the physical properties of fluidized bed granulations have also been reported (Davies and Gloor, 1972, 1973; Andreev et al., 1980; Wan and Lim, 1988; Wan et al., 1992). This paper presents the findings of employing binder solutions containing dissolved drug to produce granules in a fluidized bed granulator. This approach is rather interesting as it allows the delivery of drug simultaneous with granulation.

2. Materials and methods

2.1. Materials

Lactose monohydrate (Pharmatose 200M, DMV, The Netherlands) was used as feed material for fluidized bed granulation. The binders employed for production of granules were polyvinylpyrrolidone of various grades (Povidone K25, K29–32, K120, ISP, USA and Kollidone K90, BASF, Germany). The K-number distinguishes the different molecular weight of polyvinylpyrrolidone (PVP). In this study, the average molecular weights of PVP K25, K29–32, K90 and K120 are 26 000, 42 000, 1 100 000 and 2 000 000, respectively (Robinson et al., 1990). Propranolol hydrochloride (ICI, UK) was chosen as the model drug. Its solubility in water at room temperature (29–30°C) determined by spectrophotometric assay at 290 nm was 0.137 g/ml. The particle densities of lactose and propranolol hydrochloride using helium gas pycnometer (AccPyc, 1330, USA) were 1.5346 and 1.2236 g/cm^3 respectively.

2.1.1. Granule preparation

A load of 400 g lactose, previously sieved through a sieve of 710 μm aperture size was granulated with PVP solution in a fluidized bed granulator (Niro Aeromatic, Strea 1, Switzerland). The operating conditions for fluidized bed granulation were similar to those reported earlier (Wan et al., 1995), the atomising air pressure and inlet air temperature were 0.8 bar and 60°C respectively with a drying time of 3 min. The concentrations of different PVP grades used were 2, 3, 4, 5, 6 and 7%. The spraying rate and volume of binder solution used were 15 g/min and 200 ml respectively, unless otherwise stated. The amount of propranolol hydrochloride used was 4% based on the total powder load used for granulation. The drug was dissolved in the various concentrations and volumes of PVP K25, K29–32 and K90.

2.1.2. Viscosity

PVP solutions were prepared and left to hydrate overnight prior to viscosity determination.

The solutions were first allowed to equilibrate to the temperature of the water-bath. The flow times of PVP solutions at the stated temperature using a suspended-level viscometer (Technico No. 2, UK) were determined. Similar determinations were carried out with solutions prepared by dissolving 4% w/w of drug based on the total powder load, in 200 ml of PVP solutions. All determinations were in triplicates and average values computed. From these data, the kinematic viscosities were calculated.

2.1.3. Mass median diameter and span

A random sample of granules of approximately 120 g were subjected to a size analysis using a nest of appropriately selected sieves (Endecotts, UK) from a series of aperture sizes, 250, 355, 500, 600, 710, 850, 1000, 1180, 1400, 1700, 2000, 2800 and 3350 μm vibrated at an amplitude of 1 mm (Endecotts, EVS, UK). Preliminary studies demonstrated that a sieving time of 15 min was sufficient for effective size separation of granules. The granules retained on each sieve were weighed. From the size analysis data, mass median diameter and span of each batch of granules were determined. Span is defined as the ratio of the difference of size at the 90th and 10th percentiles to that of the mass median diameter.

2.1.4. Sphericity

Sixty granules, taken randomly from the modal size fraction of each batch of granules were used for shape characterisation using a video image analyzer (Imageplus, Dapple System, USA). The images produced were digitized and analyzed by the computer. The formfactor was obtained for each batch of granules. The formfactor is defined as $4\pi \times [\text{area}/(\text{perimeter})^2]$. A formfactor value of unity indicates a perfect circle.

2.1.5. Crushing strength

Twenty five granules taken randomly from the size fraction 710–850 μm were subjected to a crushing strength test using a tensile tester (Algol, 2252, Japan). The crushing force was applied at a rate of 2.975 mm/s. The load required to crush each granule was recorded with a digital force gauge (Aikoh, 9000 series, Japan). The mean crushing strength and standard deviation of 25 granules were calculated.

2.1.6. Drug content

Twenty samples of approximately 8 mg of granules were employed for the assay for drug content using a diode array spectrophotometer at wavelength 290 nm. The mean drug content in all cases was more than 98%.

3. Results and discussion

3.1. Viscosity of PVP solutions with and without drug

Materials such as drug dissolved in the binder solution can affect the viscosity of the resultant solution. The viscosities of PVP K90 and K120 solutions containing dissolved drug are much higher than corresponding solutions without the drug (Fig. 1). Higher viscosity binder solutions can generate larger spray droplets during atomization. This could lead to formation of large granules, which are suitable as cores for coating. Cores that are small or weak will result in an end product made up mainly of agglomerated granules or fine powder, as a result of a breakdown of the granules, during the subsequent long coating process. On the other hand, for cores that are too large, dry quenching can occur easily, due to the presence of secondary agglomerated granules. It should be pointed out that the PVP K120 concentration range that can be used to produce granules was narrow. Beyond this range, granules obtained were not satisfactory, being either too fine or of aggregate nature. The use of PVP K120 solution produced mostly large granules. It appeared that the presence of dissolved drug in this binder solution aggravated the condition causing the formation of very large granules. Hence it was not included for further studies.

3.2. Effect of PVP K25

Fig. 2 shows the changes in granule characteristics brought about by changes in concentration and volume of PVP K25 solutions containing

dissolved drug. When PVP K25 concentration was maintained constant and its volume was varied, the mass median diameter of the granules was altered. At low binder concentration (2–3% w/w), an increase in the volume of the binder solution caused an increase in granule size, gradually initially, up to 400 ml and a more abrupt increase occurring beyond 400 ml (Fig. 2a). Increasing the volume of the binder solution was effectively subjecting the feed load to a prolonged granulation process and increasing the total quantum of binding effect. This effect was not very significant when the volume of binder solution used was small, because the feed material was able to accommodate this volume. However, with increasing volume of the granulating liquid, the feed material responded through the formation of larger granules. Lactose dissolved in the large volume of binder solution, increased the plasticity of the particles and thus increased the probability of coalescence.

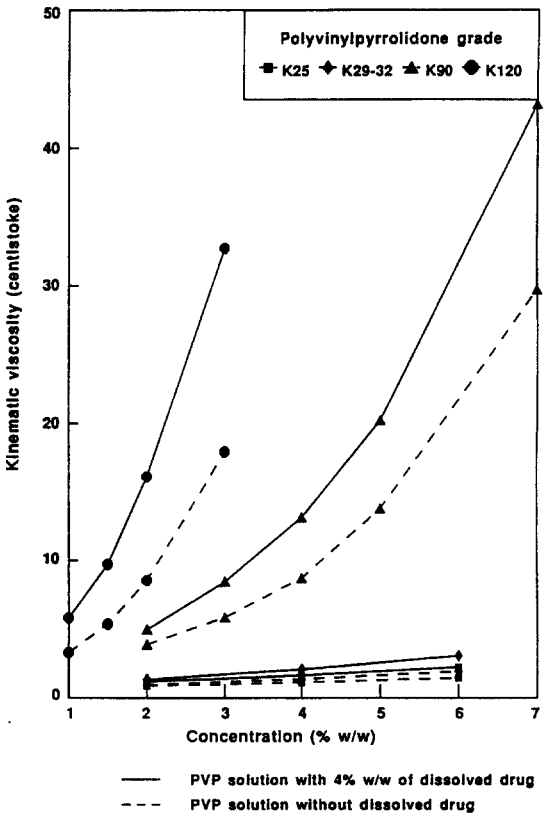

Fig. 1. Kinematic viscosities of different concentrations of various grades of PVP with and without dissolved drug, at 37°C.

There was a decrease in the value of span (Fig. 2b). The diminishing amount of fines with the increase in the binder volume was attributed to secondary agglomeration which could proceed via layering or aggregation (Fig. 2c). As the wt.% of granules smaller than 250 μm was rather high at low volumes of granulating liquid, layering effect had to be a prominent process.

With higher binder solution concentration (4–6% w/w), a different trend was observed. With increasing binder concentration, there was a steeper increase in the mass median diameter at low volumes of binder solution and then a drop in granule size as the volume was increased further. The addition of drug in a small volume of concentrated granulating solution can promote size enlargement process. The dissolved drug contributed to a rise in solution viscosity, this rise is more prominent if the drug is dissolved in a highly concentrated or a small volume of granulating solution (Fig. 3a). A large volume of dilute granulating solution does not undergo a drastic change in its viscosity when a drug is dissolved in it. The increase in the volume of binder solution of a constant concentration resulted in secondary agglomeration of primary particles. This gave rise to the increase in granule size.

The use of a greater volume of PVP solution requires a longer granulation time. Since PVP K25 solution has low binding strength, high concentration and volume of this solution were not able to produce granules that were resistant to the attrition forces operating against the formation of granules. Agglomerated particles have relatively weak interparticulate adhesive bonds when PVP K25 solution was used. They were easily broken down in the product container when fluidized. The result was a smaller mass median diameter. Although granules formed had smaller mass median diameter, the difference in the mechanical strength of granules was significant when high volume and concentration of binder solution was used (Fig. 2d). This probably prevented excessive breakdown of the agglomerated particles as the fraction of granules less than 250 μm at this point was small (Fig. 2c).

When the binder solution volume was kept constant, low and high concentrations of these

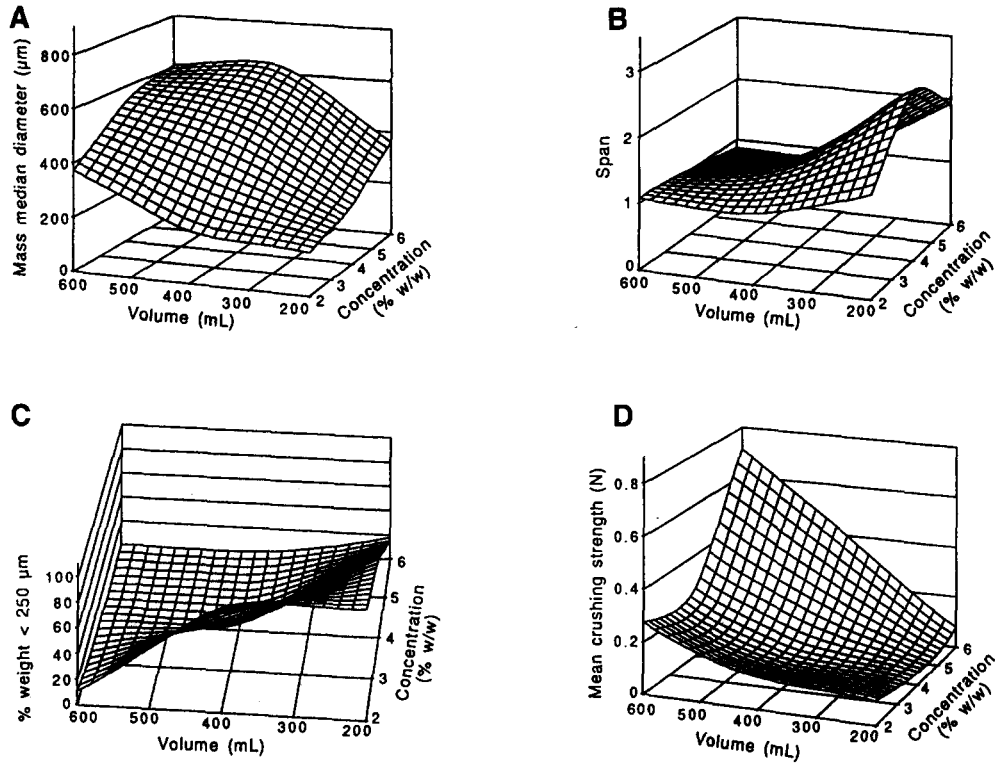

Fig. 2. Effect of concentration and volume of PVP K25 solution containing dissolved drug on (a) mass median diameter, (b) span, (c) wt.% < 250 μm and (d) mean crushing strength of granules.

solutions produced small and large granules respectively. The span value was the highest in the mid-range of binder solution concentration, it decreased at both low and high concentrations. This could be attributed to the fact that when a dilute binder solution was used, the batch consisted essentially of fine granules; with a concentrated solution, it comprised mainly larger granules (Fig. 2c). There was little change in the span value and amount of granules less than 250 μm at a high volume of the binder solution across the range of concentration studied. This indicated a collection of relatively larger granules with very little fines.

Mechanical strength of a granule is dependent on its structural framework. A greater amount of binder will impart a greater mechanical strength to the granules. This is demonstrated by the data from the mean crushing strength of granules (Fig. 2d). The higher values are associated with the higher concentration and larger volume of the binder used. These two factors lead to more binder being deposited on the granules, which when dried would manifest as solid bonds, holding the feed material together. The tenacity of this structural framework was enhanced by the presence of more binder.

3.3. Effect of PVP K29–32

Granules produced with PVP K29–32 solutions (Fig. 4) showed similar trend in their characteristics to those formed with PVP K25 solutions (Fig. 2). These two binder solutions, with or without dissolved drug exhibited a small increase in their viscosities in the range of concentration studied (Fig. 1). Fig. 4a shows a sharp drop in the granule mass median diameter when high concentration and volume of the binder solution was used. This polymer grade was able to bring about a faster rate of size enlargement process when compared

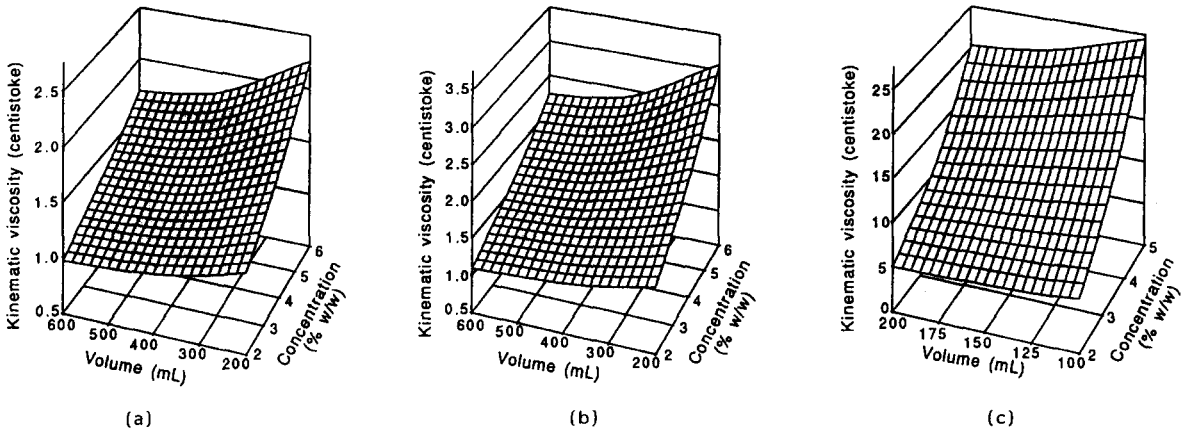

Fig. 3. Change in kinematic viscosities with volume and concentrations of (a) PVP K25, (b) PVP K29–32 and (c) PVP K90 solutions containing 4% w/w of dissolved drug measured at 37°.

with PVP K25. Although the adhesive strength of PVP K29–32 was higher than that of PVP K25 solution, it was, however, not sufficiently high to resist the breakup forces generated in the fluidized bed granulator. The effect of attrition was pronounced at high concentration and volume of binder solution, it should be noted that granulation time was correspondingly longer, resulting in a lower mass median diameter.

It is believed that the predominant size growth mechanism for low binder solution concentration is layering. As the molecular weight of the polymer is increased, the effect of the aggregation process to produce multiparticulate granules becomes more significant. In the use of PVP K29–32, it would seem that the process of aggregate agglomeration would be slightly predominant. The agglomerated particles existed on bonds holding the component particles together at the contact surfaces. These agglomerated particles could be broken down. Compounded with the longer granulation time associated with the high concentration and large volume of binder solution, the opposing effect could become very significant indeed. This explains the decrease in the mass median diameter of granules produced with high concentration and volume of binder solution.

Although there was continuous breakup of agglomerated particles, the component particles were still significantly large. As such, it did not cause an increase in the span value (Fig. 4b). This was evident by the small proportion of granules less than 250 μm when high concentration and volume of PVP K29–32 solutions were used. There was a difference in the plots of the span values for granules prepared using PVP K25 and PVP K29–32 solutions (Fig. 2b and Fig. 4b). The span value at the mid-range concentration and small volume of granulating liquid (200 ml) used was high for granules with PVP K25 but low for those with PVP K29–32. When a small volume of PVP K29–32 solution (200 ml) was used, it was capable of rapidly granulating the feed material to produce some agglomerated particles as the drug dissolved in this small volume of solution increased the concentration of the resulting solution. A large proportion of the granulated product still consisted of very small granules. However, the larger granules could affect the size distribution of a granule batch by increasing the span value. As the concentration increased further for 200 ml granulating solution, the proportion of smaller particles dropped. This was also indicated by the span value which decreased and then remained almost constant.

The crushing strength plots for these granules (Fig. 4d) showed a similar pattern to that of granules prepared with PVP K25 solutions (Fig. 2d), although the values were larger for those granulated with PVP K29–32 solution under

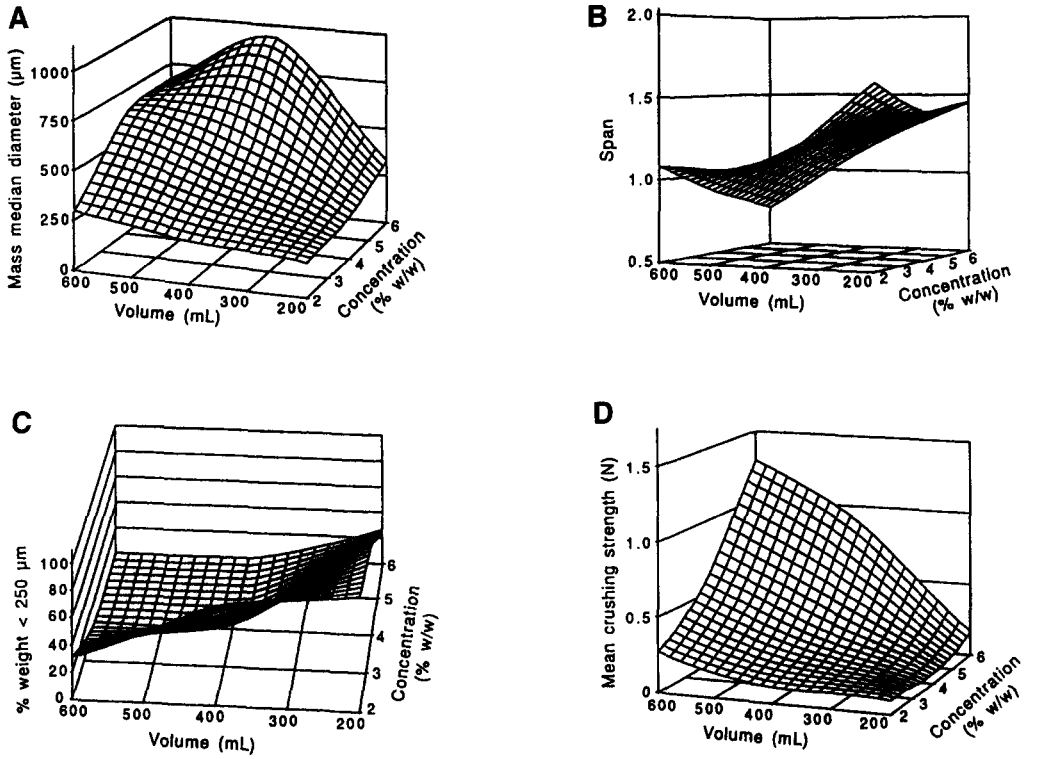

Fig. 4. Effect of concentration and volume of PVP K29–32 solution containing dissolved drug on (a) mass median diameter, (b) span, (c) wt.% < 250 μm and (d) mean crushing strength of granules.

comparable processing conditions. This was due to the higher viscosity grade polymer being able to impart greater binding power and thus greater granule strength. The use of a greater volume or a higher concentration of binder solution rendered the granules more resistant to crushing force.

3.4. Effect of PVP K90

PVP of high molecular weight, such as PVP K90 can confer strong bonds to the granules and thus enable them to better withstand the effects of attritive forces generated during fluidized bed granulation. Thus, the opportunity for size growth is greatly enhanced. As such, the mass median diameter of granules prepared with PVP K90 was higher compared with that of granules from the lower molecular weight PVP solutions using the same conditions (Fig. 2a, 4a, 5a). The stronger cohesive forces within the granules played a major role in reducing the proportion of fine granules, which can be due to unagglomerated powders or deagglomeration of agglomerated particles and breakdown of granules (Pell, 1990). This is illustrated by the plot in Fig. 5b, in which a comparatively low span value was obtained across the different combination of process conditions used, except when a low concentration combined with a low volume of binder solution was employed for granulation. At this combination of process conditions, the mass median diameter was the lowest. There was also the presence of a relatively high proportion of granules smaller than 250 μm, although this proportion was less than the corresponding batches of granules produced using PVP K25 and PVP K29–32 solutions containing dissolved drug and the corresponding PVP K90 solution without dissolved drug (Figs. 2 and 4–6).

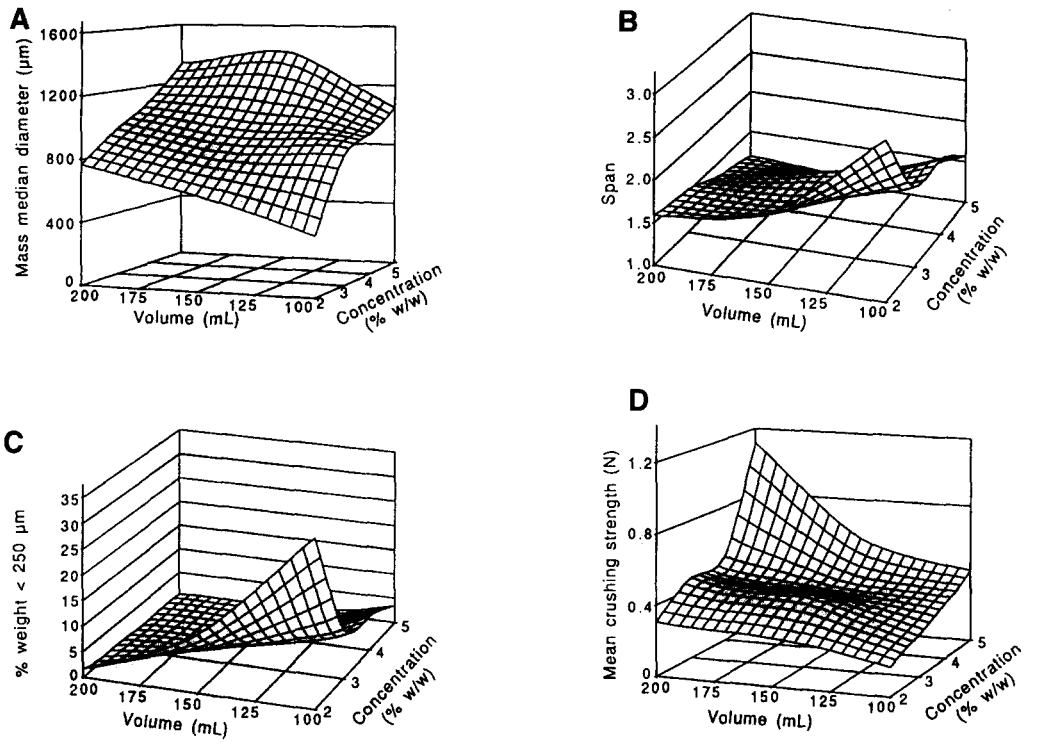

Fig. 5. Effect of concentration and volume of PVP K90 solution containing dissolved drug on (a) mass median diameter, (b) span, (c) wt.% < 250 μm and (d) mean crushing strength of granules.

Fig. 5d shows the mean crushing strength values of granules produced with different PVP K90 solution concentrations and volumes. A trend similar to that of granules produced with the other PVP grade was observed, but the mean crushing strength value of granules granulated with PVP K90 solution was quantitatively higher when all other process parameters were the same. The increase in mechanical strength of granules was significant at high concentration and volume of binder solution used.

Fig. 6 shows the characteristics of granules produced using PVP K90 solutions with and without dissolved drug. The use of 100 ml PVP K90 solution (Fig. 6a) containing dissolved drug resulted in granules that have mass median diameter approximately doubled that of corresponding granules produced with PVP K90 solution without the dissolved drug. With an increase to 150 ml, there was a further increase in the mass median diameter. However, the granule size decreased slightly after this point. Binder solutions containing drug consistently produced granules that were larger than granules of the corresponding solution without the dissolved drug. The dissolved drug can form crystalline bonds on drying, helping in the agglomeration process. The viscosity profiles in Fig. 3 may provide an answer to this observation. A higher viscosity binder solution formed larger droplets when atomized. This led to larger granules being formed. The increase in the volume of the binder solution with dissolved drug would cause larger granules to be produced. This was only applicable up to a certain volume of binder solution. Drug dissolved in additional volume of binder solution did not affect the viscosity of the resultant solution as much as that dissolved in smaller volumes (Fig. 3). The effect of the dissolved drug on solution viscosity has been evident when the binder volume used was increased. Hence, there was a small change in the mass median diameter.

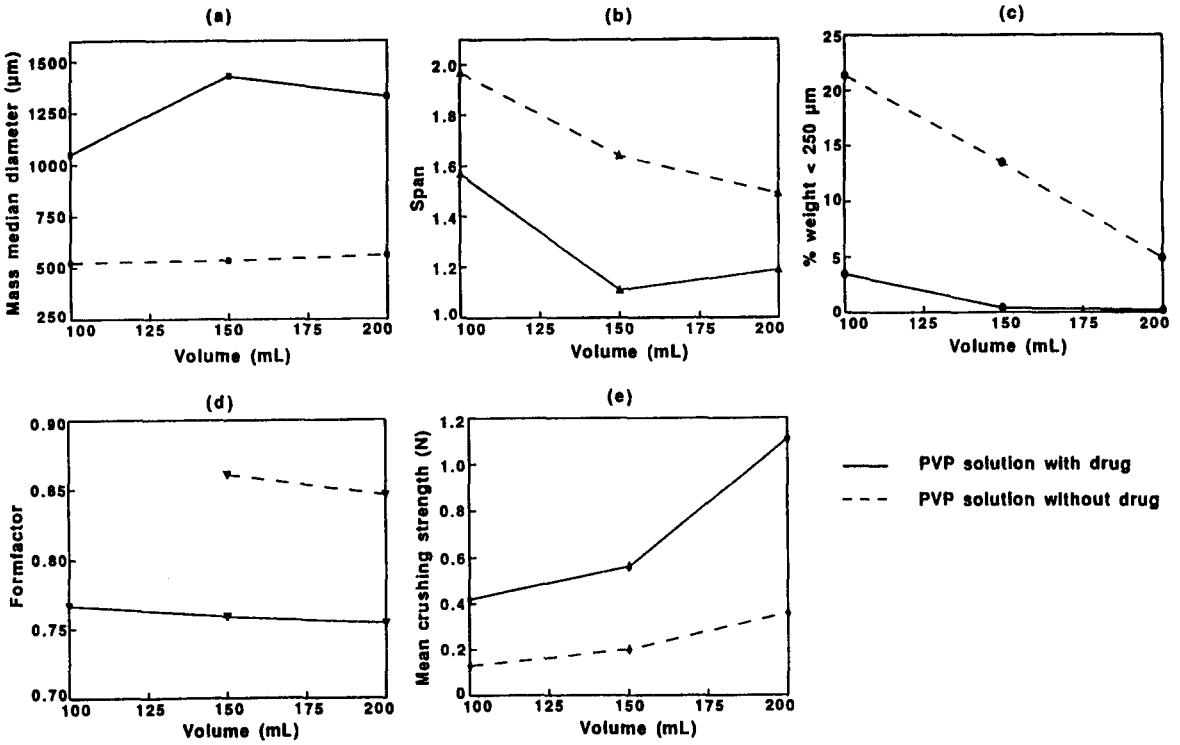

Fig. 6. Characteristics of granules produced with PVP K90, 5% w/w solution.

The span values of granules containing drug were lower than those of corresponding granules without the incorporation of drug. The trend of the span values is the opposite to that of the mass median diameter, whereby a batch of high mass median diameter granules have a lower span value. This also applies to the amount of granules smaller than 250 μm, in which case this was low and less than 5%. These granules were able to retain their integrity during the granulation process as could be observed from the higher mechanical strength of granules in Fig. 6e.

Granulation with PVP K90 solution is thus very efficient with all the feed material coming into contact with the binder solution. Nevertheless, a more efficient granulation may mean the presence of secondary agglomeration with the production of multiparticulate granules. When this occurs, granules with a lower degree of sphericity will be produced (Fig. 6d).

4. Conclusion

The effect of PVP of varying molecular weight on the mass median diameter, span, wt.% < 250 μm as well as crushing strength was related to the concentration and volume of PVP solution used. An extended granulation process, consequent from the application of a larger volume of binder, enhanced the binding effect. A resultant response is production of larger granules, a decrease in span and wt.% < 250 μm with an increase in crushing strength values. Size enlargement in this case may be attributed to secondary agglomeration and layering is the dominant process.

References

Andreev, B.V., Gorodnichev, V.I., Minina, S.A. and El-Banana, H.M., Granule growth of pharmaceutical powders in a fluidised bed. *Pharm. Ind.*, 42 (1980) 1304–1306.

Aulton, M. and Banks, M., The factors affecting fluidised bed granulation. *Manuf. Chem. Aerosol News*, 49 (1978) 50–56.

Davies, W.L. and Gloor, W.T. Jr., Batch production of pharmaceutical granulations in a fluidised bed II: effect of various binders and their concentrations on granulation and compressed tablets. *J. Pharm. Sci.*, 61 (1972) 619–622.

Davies, W.L. and Gloor, W.T. Jr., Batch production of pharmaceutical granulation in a fluidised bed III: binder dilution effects on granulation. *J. Pharm. Sci.*, 62 (1973) 170–171.

Kristensen, H.G., Agglomeration of powders. *Acta Pharm. Suec.*, 25 (1988) 187–204.

Lipps, D.M. and Sakr, J.P.S., Characterisation of wet granulation process parameters using response surface morphology I. Top-spray fluidised bed. *J. Pharm. Sci.*, 83 (1994) 937–947.

Mehta, A., Adams, K., Zoglio, M.A. and Carstensen, J.T., Influence of granulation liquid flow rate on particle size distribution in spray-granulated products. *J. Pharm. Sci.*, 66 (1977) 1462–1464.

Olsen, K.W. and Mehta, A.M., Fluid bed agglomeration and coating technology-state of the art. *Int. J. Pharm. Technol. Prod. Manuf.*, 6 (1985) 18–24.

Pell, M., *Handbook of Powder Technology*, Vol. 8, Elsevier, Amsterdam, 1990.

Rankell, A.S., Scott, M.W., Lieberman, H.A., Chow, F.S. and Battista, J.V., Continuous production of tablet granulation in a fluidised bed II: Operation and performance of equipment. *J. Pharm. Sci.*, 53 (1964) 319–324.

Robinson, B.V., Sullivan, F.M., Borzelleca, J.F. and Schwartz, S.L., *A Critical Review of the Kinetics and Toxicology of Polyvinylpyrrolidone (Povidone)*, Lewis, Michigan, 1990.

Schaefer, T., Equipment for wet granulation. *Acta Pharm. Suec.*, 25 (1988) 205–228.

Schaefer, T. and Worts, O., Control of fluidised bed granulation I: effects of spray angle, nozzle height and starting materials on granule size and size distribution. *Arch. Pharm. Chem. Sci. Ed.*, 5 (1977a) 51–60.

Schaefer, T. and Worts, O., Control of fluidised bed granulation II: estimation of droplet size of atomized binder solutions. *Arch. Pharm. Chem. Sci. Ed.*, 5 (1977b) 178–193.

Schaefer, T. and Worts, O., Control of fluidised bed granulation III: effects of inlet air temperature and liquid flow rate on granule size and size distribution. Control of moisture content of granules in the drying phase. *Arch. Pharm. Chem. Sci. Ed.*, 6 (1978a) 1–13.

Schaefer, T. and Worts, O., Control of fluidised bed granulation IV: effects of binder solutions and atomization on granule size and size distribution. *Arch. Pharm. Chem. Sci. Ed.*, 6 (1978b) 14–25.

Schaefer, T. and Worts, O., Control of fluidised bed granulation V: factors affecting granule growth. *Arch. Pharm. Chem. Sci. Ed.*, 6 (1978c) 69–82.

Schwartz, J.B., Granulation. *Drug. Dev. Ind. Pharm.*, 14 (1988) 2071–2090

Wan, L.S.C. and Lim, K.S., The effect of incorporating polyvinylpyrrolidone as a binder on fluidised bed granulation. *S.T.P. Pharma Sci.*, 4 (1988) 560–571.

Wan, L.S.C., Heng, P.W.S. and Muhuri, G., Analysis of growth of granules in a fluidised bed granulator, *S.T.P. Pharma Sci.*, 2 (1992) 381–386.

Wan, L.S.C., Heng, P.W.S. and Ling, B.L., Fluidised bed granulation with PVP K90 and PVP K120. *Drug Dev. Ind. Pharm.*, 21 (1995) 857–862.

Zenz, F.A., *Handbook of Powder Science and Technology*, Van Nostrant Reinhold, New York, 1984.