Drug Development and Industrial Pharmacy, 23(6), 611–618 (1997)

COMMUNICATION

Effect of Binder Level and Granulating Liquid on Phenylbutazone Pellets Prepared by Extrusion–Spheronization

J. Varshosaz,* R. A. Kennedy, and E. M. Gipps

Department of Pharmacy, University of Sydney, 2006, NSW, Australia

ABSTRACT

The effects of type and amount of binding agent and different amounts of granulating liquid on the physical properties of uncoated beads of phenylbutazone were investigated. The binders used were polyvinylpyrrolidone (PVP) and gelatin/starch (G/S) at two levels, and each formulation at two percentages of granulating liquid; water/ethanol at 60/40 ratio. The ability of these binders to produce pellets of phenylbutazone by the extrusion–spheronization method was evaluated by two criteria. The first was physical properties such as particle size, yield between 710 and 1400 μm, friability, and density. The other criterion was the drug release profile. Generally 5% of gelatin/starch with 80% of solvent produced more uniform pellets with a narrower particle size range and a high yield of spheres between 710 and 1000 μm. Changing the type of the binder, its percentage, and the amount of granulating liquid had no significant effect on the pellet density. Changing the type of the binder or/and its percentage and also the effect of granulating liquid in combination with the other mentioned variables had significant effects on the friability of the pellets. The results show that the amount of granulating liquid and binder amount have the same influence on the drug release from pellets. A slower release rate was observed with increased amounts of these two variables. These differences in the release profiles were parallel to the differences in hardness and structure of the pellets. The difference between particle diameter and the percentage of drug released within 30 min was significant in all formulations.

*To whom correspondence should be addressed at Faculty of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Iran.

INTRODUCTION

The methods of manufacturing pellets include crystallization; agglomeration by tumbling, compacting, and crushing; and extrusion–spheronization (1). Extrusion–spheronization is extensively used for a wide range of drugs since the cores produced, whether for encapsulation or tableting, have some advantages. Spherical pellets with smooth surfaces, a narrow particle size distribution, minimal friability, and suitable density are able to mix and flow well, and are able to incorporate high levels of active substances, up to 60–80%. Pelletization of drugs may also allow control of a dissolution profile (2,3).

The number of excipients available for extrusion–spheronization is limited. Microcrystalline cellulose and lactose are well-known excipients for pellet production (2). In some cases the addition of binders may be necessary to produce acceptable spheres (4).

Among the different agents used as binders in extrusion–spheronization, there are reports on using sodium carboxymethyl cellulose (5) and chitosan (6).

The effect of some common granule binding agents on production of pellets by the extrusion–spheronization technique was investigated. Phenylbutazone was used as a water-insoluble model drug and Avicel PH 101/lactose in a 2/1 ratio was used as the base formulation. Polyvinylpyrrolidone (PVP) and a mixture of gelatin and starch were used at the lowest and highest levels commonly employed in granule production, namely 2% and 5%. As the amount of liquid used in the wet granulation stage has an important role in the friability of the pellets (7), the effect of the binders with two levels of the liquid was studied.

MATERIALS

Phenylbutazone BP, microcrystalline cellulose (Avicel PH 101, FMC Corporation USA)
Lactose BP (Wynvale, New Zealand)
Polyvinylpyrrolidone (PVP, MW 40000, Sigma Chemical Company, USA)
Gelatin (food grade)
Maize starch BP (Fielders, England)

All other ingredients were at least reagent grade and were used as supplied.

METHODS

Preparation of Pellets

The different formulations used are summarized in Table 1. The manufacturing process is shown schematically in Fig. 1. PVP was added to the other powders as the dry form. Gelatin and starch 50/50 was added as a 25% w/v aqueous solution and then the whole mass was wet granulated with an ethanol-in-water solution whose strength was adjusted so that the final water-to-ethanol ratio was 60/40. The mass of wet granulated mixture was extruded for 10 min, and the extrudates were spheronized for 5 min. The spheres were dried for 2 hr at 37°C in a convection oven. Each batch was manufactured in triplicate.

Evaluation of Pellets (8)

Particle size analysis was determined using a vibratory sieve shaker (Retsch, Vibro, Germany) with a set

Table 1

Composition of Phenylbutazone Microspheres Prepared by Extrusion–Spheronization

Ingredients (for 100 g of Pellets)	Level I of Binder (g)	Level II of Binder (g)
Phenylbutazone	20	20
Binder (PVP or G/S)	2	5
Avicel (PH 101)	52	50
Lactose	26	25
Water/ethanol: 60/40	80 and 90	80 and 90

Note. PVP = polyvinylpirrolidone; G/S = gelatin/starch:50/50.

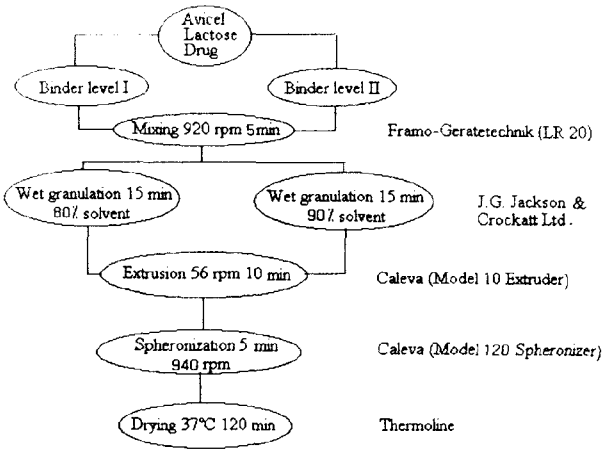


Figure 1. Processing flow chart of extrusion–spheronization.

of 7 sieves. Each sample was sifted for 10 min at a speed position of 10, and the weight percent retained on each sieve was recorded.

The shape of individual pellets from sieve fraction 710–1000 μm was visualized by scanning electron microscopy (Jeol 35C, Japan).

To determine the friability, a sample of each formulation was sieved for 10 min on the vibratory shaker and the 710- to 1000-μm fraction was separated. This was rotated for 10 min in an Erweka friabilitator tester. At the end the material was sieved again with the same method to separate the fines. The weight reduction was recorded as the percentage.

Bulk density was measured using Fonner's method (9). Fifty grams of the pellets were placed in a 100-ml graduated cylinder, which was dropped 20 times from a height of 1.9 cm onto a hard surface. The volume of particles was measured to the nearest 0.5 ml and the bulk density was calculated.

A nitrogen pycnometer (Multivolume 1305, Micromeritics Co., USA) with a 5-cm^3 sample holder was used to obtain the true density. Porosity was calculated by Eq. (1), as a measure of ease of water penetration into the pellets and also of the degree of close orientation of the pellets because of the regular spherical shape. This methodology does not account for any fully enclosed pore.

$$\text{Porosity } \% = [(\text{true density} - \text{bulk density})/\text{true density}] \times 10 \quad (1)$$

Drug release studies were performed on a sieve fraction 710–1000 μm, in a six-pot dissolution apparatus (Vankel VK 6010, USA) by the paddle method of USP/NF XXI in 900 ml of potassium phosphate buffer 0.2 M (pH = 7.4) at 100 rpm and 37°C. Dissolution test samples were analyzed spectrophotometrically (Hitachi U 2000, Japan) at 264 nm.

The experimental design was 2^3 factorial, and the results were analysed by analysis of variance (ANOVA) using a computer package (Statview 4 for Macintosh, Abacus Concepts, USA). The critical level of significance chosen was $p < 0.01$, and Fisher's PLSD was used for post hoc testing.

RESULTS AND DISCUSSION

Using the formulations shown in Table 1 and the processing flow chart shown in Fig. 1, pellets were produced by extrusion–spheronization. The results of physical tests for each formulation are shown in Table 2, with the statistical analysis results shown in Table 3. Pellets containing PVP showed a narrower particle size distribution compared to those prepared with G/S, as shown in Fig. 2. All but one formulation prepared with PVP had the highest yield at the particle size range between 710 and 1400 μm; of pellets produced by P22, 98% were larger than 1400 μm. However, all G/S formulations had their highest yield at 710–1400 μm. This may be related to the greater tackiness of PVP compared to G/S.

Increasing the binding agent from 2% to 5% had a significant effect on the particle size distribution. Granulating liquid amount had a similar effect. Simultaneously, increasing the binder percentage and increasing the amount of granulating liquid increased the particle size distribution significantly. The type of the binder also had a significant effect on this property. The pellets produced by PVP had a smaller mean particle size compared to G/S.

The morphology of the pellets is shown in Fig. 3. As this figure indicates, there are some fractures on the surface of the pellets containing PVP while G/S produced a smoother surface. Except for formulation P22, the majority of the pellets produced were spherical. In P22 the pellets were rod shaped, possibly because of their high resistance to being spheronized.

Increasing the granulating fluid at a particular level of each type of binder decreased the friability significantly, while increasing the binder level for both bind-

Table 2

Physical Properties of Phenylbutazone Pellets [Mean Values (SD)] Using Different Amounts of Granulating Liquid and Binders [Polyvinylpyrrolidone (PVP) and Gelatin/Starch: 50/50 (G/S)] Prepared by Extrusion-Spheronization

Binder Type	Binder %	Granulating Liquid %	Formulation Code	Granule Diameter (mm)	Bulk Density (g/cm^3)	True Density (g/cm^3)	Friability (%)	Total Porosity (%)	Drug Released (% in 30 min)
PVP	2	80	P11	0.887 (0.125)	0.526 (0.009)	1.45 (0.13)	3.62 (0.82)	63.56 (2.86)	92.7 (1.4)
	2	90	P12	0.758 (0.011)	0.555 (0.008)	1.45 (0.06)	5.63 (0.72)	61.69 (1.09)	76.5 (3.8)
	5	80	P21	0.857 (0.019)	0.627 (0.018)	1.34 (0.08)	1.62 (0.36)	53.07 (3.62)	84.1 (1.2)
	5	90	P22	1.427 (0.008)	0.686 (0.016)	1.35 (0.13)	0.71 (0.15)	49.25 (5.08)	42.8 (0.6)
GS	2	80	GS11	0.918 (0.004)	0.577 (0.041)	1.42 (0.09)	0.99 (0.14)	59.36 (1.40)	72.9 (1.8)
	2	90	GS12	0.769 (0.013)	0.600 (0.013)	1.42 (0.10)	2.91 (0.23)	57.58 (3.52)	68.8 (4.6)
	5	80	GS21	0.872 (0.026)	0.635 (0.042)	1.46 (0.10)	1.15 (0.11)	56.36 (4.32)	67.5 (1.0)
	5	90	GS22	0.921 (0.018)	0.702 (0.041)	1.45 (0.12)	1.31 (0.23)	51.49 (2.34)	59.7 (2.5)

Table 3

Probabiliy of Factors Affecting Characteristics of Phenylbutazone Pellets Prepared by Extrusion–Spheronization: Analysis Performed by 2^3 Factorial ANOVA

Factors and Interactions	Granule Diameter (mm)	Bulk Density (g/cm^3)	True Density (g/cm^3)	Friability (%)	Drug Released (% in 30 min)
Binder type	<0.0001	0.0167	0.3844	<0.0001	<0.0001
% Binder	<0.0001	<0.0001	0.4496	<0.0001	<0.0001
Binder × % binder	<0.0001	0.1285	0.1270	<0.0001	<0.0001
% liquid	<0.0001	0.0011	0.9532	0.0003	<0.0001
Binder × % liquid	<0.0001	0.9650	0.8603	0.1811	<0.0001
% binder × % liquid	<0.0001	0.1189	0.9532	<0.0001	<0.0001
Binder × % binder × % liquid	<0.0001	0.7593	0.8603	0.1174	<0.0001

Note. p values < 0.01 are significant.

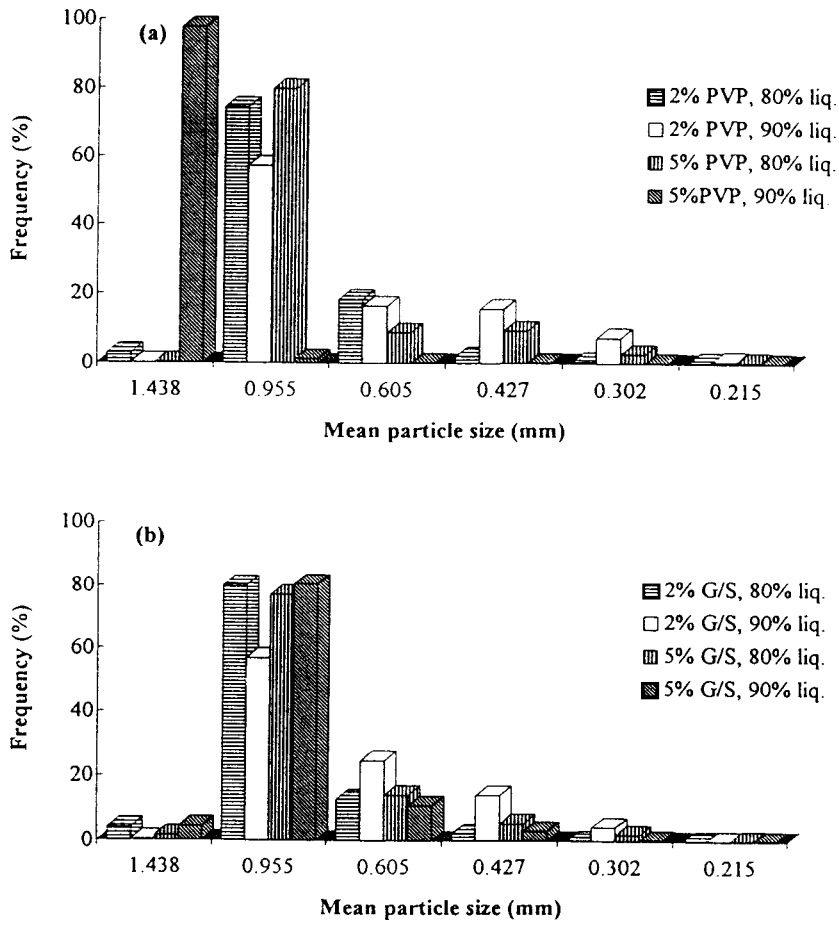
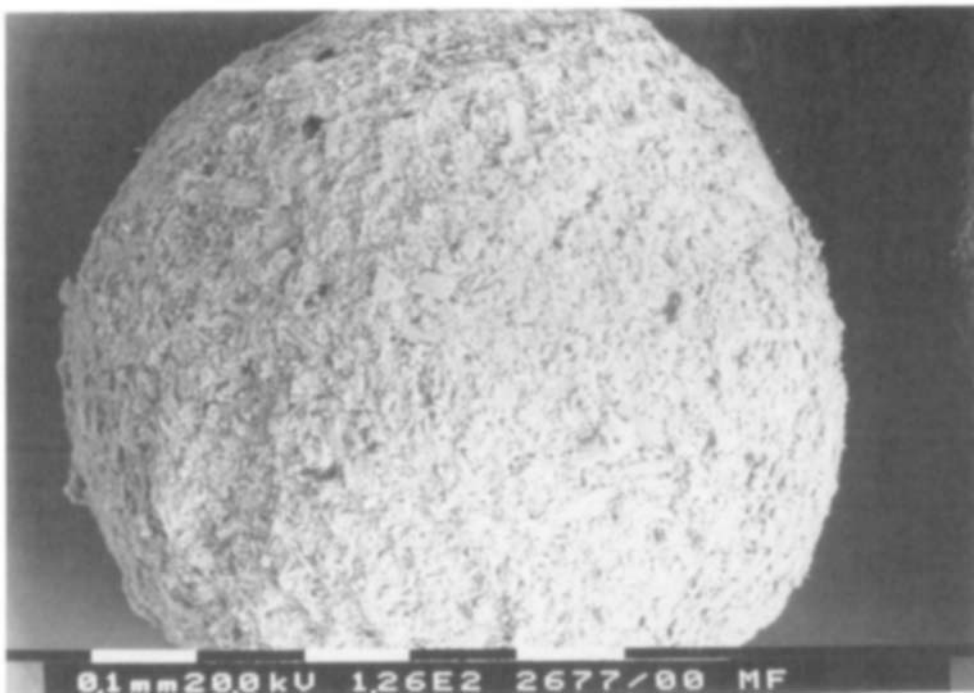


Figure 2. Weight-size distribution of phenylbutazone pellets containing different amounts of binders and solvent: (a) polyvinylpyrrolidone (PVP); (b) gelatin/starch (G/S).

(a)



(b)

Figure 3. Scanning electron micrographs of phenylbutazone pellets containing different types of binders: (a) polyvinylpyrrolidone (PVP); (b) gelatin/starch (G/S).

ers decreased the friability significantly. Generally pellets prepared with G/S showed less friability compared to PVP.

None of the variables discussed so far had a significant effect on the true density. The bulk density was affected by increasing the binder percentage from 2% to 5%. This may be attributed to more uniform spherical pellets produced by increasing the binder amount, since nearly spherical particles lead to higher bulk or tap density (10).

The drug release profiles of different formulations of PVP and G/S are shown in Fig. 4. As indicated, changing the percentage of the binder and/or the granulating liquid had a significant effect on the drug dissolved within 30 min. Changing the binder type from PVP to G/S, or binder percentage from 2% to 5%, or the amount of liquid from 80% to 90% significantly decreased the amount of drug dissolved within 30 min. This also shows the binding effect of the granulating liquid. Therefore increasing the granulating liquid and/or binder increases the hardness of the pellets (Table 2) and so prolongs drug release rate (Fig. 4).

CONCLUSIONS

It can be concluded that by increasing the percentage of the binder and/or granulating liquid, a prolonged drug release effect may occur. Gelatin/starch had a greater effect than polyvinylpyrrolidone on the binding properties of the microspheres produced by extrusion–spheronization. For both binders, an increase in the amount of binder or the percentage of granulating liquid caused significant decrease in the dissolution rate of the drug. However, increasing both variables—i.e., the binder (polyvinylpyrrolidone or gelatin/starch) and

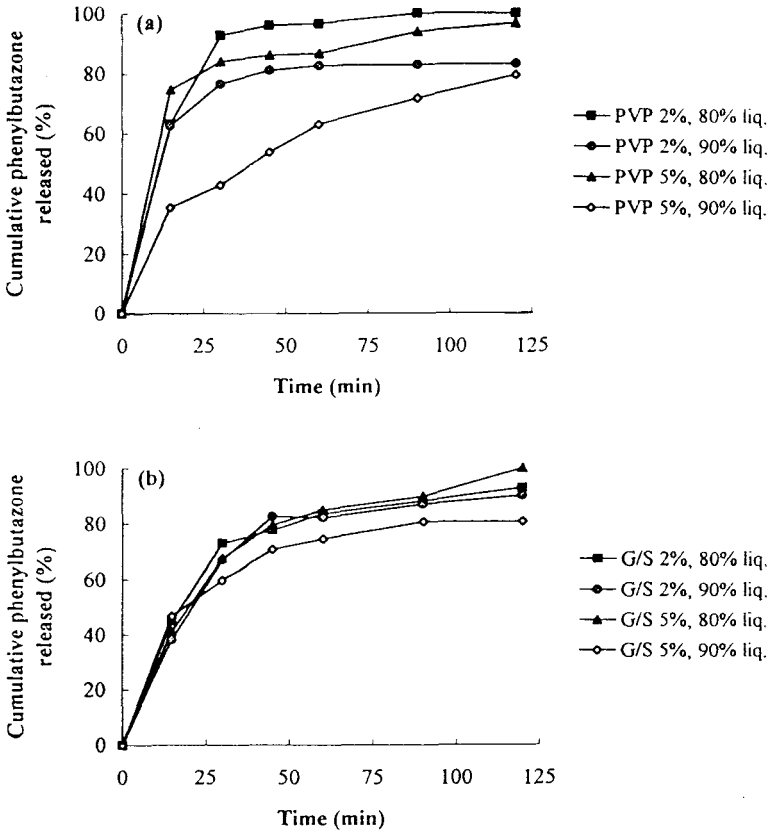


Figure 4. Dissolution profiles of phenylbutazone pellets containing different amounts of binders and solvent in phosphate buffer (pH = 7.4): (a) polyvinylpyrrolidone (PVP); (b) gelatin/starch (G/S).

granulating liquid—simultaneously may increase the hardness of the pellets greatly and prolong the drug release rate.

REFERENCES

1. C. Eskilson, Manuf. Chem., 3, 33 (1985).
2. C. Vervaet, L. Baert, and J. P. Remon, Int. J. Pharm., 116, 131, (1995).
3. A. M. Dyer, K. A. Khan, and M. E. Aulton, Drug Dev. Ind. Pharm., 20(20), 3045 (1994).
4. J. A. B. Funck, J. B. Schwartz, W. J. Reilly, and E. S. Ghali, Drug Dev. Ind. Pharm., 17, 1143 (1991).
5. J. A. C. Elbers, H. W. Bakkenes, and J. G. Fokkens, Drug Dev. Ind. Pharm., 18(5), 501 (1992).
6. S. R. Goskonda and S. M. Upadrashta, Drug Dev. Ind. Pharm., 19(8), 915 (1993).
7. L. Baert and J. P. Remon, Int. J. Pharm., 95, 135 (1993).
8. I. Ghebre-Sellassie, *Pharmaceutical Pelletization Technology*, Marcel Dekker, New York, 1989, p. 241.
9. D. E. Fonner, Jr., G. S. Banker, and J. Swarbrick, J. Pharm. Sci., 55, 181 (1966).
10. L. Lachman, H. A. Lieberman, and J. L. Kanig, *The Theory and Practice of Industrial Pharmacy*, Lea & Febiger, Philadelphia, 1986, p. 77.