International Journal of Pharmaceutics, 15 (1983) 97–111
Elsevier Biomedical Press

The influence of granulating fluids upon granule and tablet properties: the role of secondary binding

James I. Wells * and Clive V. Walker

Beecham Pharmaceuticals, Yew Tree Bottom Road, Epsom, Surrey (U.K.)

(Received June 7th, 1982)
(Modified version received November 8th, 1982)
(Accepted November 10th, 1982)

Summary

The influence of binder vehicle upon granule and tablet properties has been studied in a model system containing acetylsalicylic acid (aspirin) and polyvinylpyrrolidone as binder. Using a range of ethanol : water mixtures as binder vehicles, large differences in drug solubility and binder properties were obtained.

Greater drug solubility produced larger granules with tighter distributions and reduced friability. Wettability controlled granule growth whereas binder viscosity was not fundamentally important. The surface tension of the binder controlled granule bulk density.

The friability of the tablets was not reduced by secondary binding caused by solute deposition but was simply related to tablet tensile strength. High drug solubility in the binder produced tablets with poor disintegration properties. The volatility of the binder vehicles controlled the size of the redeposited acetylsalicylic acid crystals, and fine crystals appeared to block the tablet capillary network.

Introduction

Granulation is widely used to improve flow, prevent segregation and enhance the compressibility of a drug prior to tableting. The theory of granulation may be divided into binding mechanisms (Rumpf, 1958) and granule growth and formation (Newitt and Conway-Jones, 1958). In wet granulation, hardening binders and

* Present address to which correspondence should be addressed: Pharmaceutical Research and Development, Pfizer Central Research, Sandwich, Kent, U.K.

0378-5173/83/0000-0000/$03.00

recrystallization are the most common binding mechanisms. The use of soluble adhesive materials (binders) causes particle agglomeration and the properties of the granules are governed by the type of binder and its distribution within the aggregates (Seager et al., 1979). Recrystallization of soluble substances produces solid bridges at points of particle contact during drying.

The mechanisms of granule formation and growth may be divided into 3 stages (Barlow, 1968). In nucleation, granule formation begins when loose agglomerates or single particles are wetted by the binder solution and form small granules by pendular bridging. Further addition of binder and mixing consolidates the powder bed and capillary bridging forms nuclei. In the transition stage, these nuclei grow by two mechanisms: single particle addition to a nucleus by pendular bridging; or the coa'ition of two or more nuclei. At this stage the granule size is relatively small and the distribution is wide. In the final, ball growth phase, further granule enlargement occurs by the breaking of two or more granules and then combination with small granules (Newitt and Conway-Jones, 1958); by coalescence of two or more granules independently of size (Kapur and Fuerstenau, 1966) or by the distribution of fragments and particles onto large granules (Capes and Danckwerts, 1965).

The process of wet granulation is dependent on the wetting ($\cos \theta$) of the powder by the granulating fluid; the surface tension (γ) of the lenticular bridge films formed, and the viscosity (η) of the solution, since this will influence the dispersion of the binder during the mixing stage. During wet massing and the early stages of drying, the drug and any soluble excipients will dissolve and then recrystallize forming solid interparticulate bridges as the binder vehicle is evaporated. The strength of the crystalline bridges not only depends on the amount deposited but also the crystallization rate since this will influence their structure. If the drying rate is slow then large crystals will develop and influence dissolution rate, and if the void space is completely filled with binder solution, the solute will recrystallize at the surface of the wet granule, form a crust and reduce drying and change the tensile strength of the granules (Pietsch, 1969).

Accordingly changing the binder solvent may have a profound effect upon: (i) granule formation and growth during the wet massing phase (if this produces changes in the physical properties of the binder); and (ii) the structure of the granules (if the drug is soluble in the vehicle and where the evaporation rate of the solvent is changed).

In wet massing, although water is the most widely used binder vehicle, non-aqueous solvents are often used if the drug is readily hydrolyzed or thermolabile. Some work has been published on binders per se (vide: Healey, 1976) but surprisingly nothing has been reported on the effect of changing the binder vehicle. This change in solvent may alter the solubility of the drug and excipients in the binder during wet massing and affect granule structure and strength by inducing solute migration and bridging with consequent changes in tablet properties.

This paper reports the effect of wet massing acetylsalicylic acid with aqueous and aquo-alcoholic solutions of polyvinylpyrrolidone. Granule and tablet properties have been examined and related to the physical and solvent properties of the binder solutions.

Materials and Methods

Materials

Acetylsalicylic acid (fine crystals; Graesser Salicylates, Sandycroft)
Polyvinylpyrrolidone (PVP; Kollidon 90, V. Blagden, Croydon)
Cross-linked PVP (Polyplasdone XL; GAF, Manchester)
Magnesium stearate (Durham Raw Materials, Durham)
Ethanol (absolute) (J. Burroughs, London)

Methods

(i) Granulation and tableting

Acetylsalicylic acid was chosen as a model drug since it is poorly water soluble, but freely soluble in ethanol. Polyvinylpyrrolidone is widely used as a tablet binder and was chosen since it is freely soluble in water and alcohol. Cross-linked PVP was selected since it is an efficient swelling and capillary disintegrant (Stoopak and Bates, 1973) but more importantly, is completely insoluble and would not therefore interfere with drug solubility effects. Granules were lubricated with 0.5% magnesium stearate prior to tableting. It is well known that acetylsalicylic acid is unstable in the presence of metal stearates (Maudling et al., 1968) and accordingly evaluation of the tablets was completed within 48 h of preparing the compression mix. Tablets were compressed on a single punch tableting machine (Manesty F3; Speke) with 10 mm flat-bevelled tooling at 150, 225 and 300 $MN \cdot m^{-2}$ using the following formulation: acetylsalicylic acid 300 mg; cross-linked PVP 30; PVP 6; magnesium stearate 0.5% extragranular.

300 g acetylsalicylic acid and 30 g Polyplasdone XL were blended for 5 min in a tumble mixer (Turbula; Glen Creston, London) and then transferred to a small planetary mixer (Kenwood, London); 100 ml of 6% w/w solutions of PVP in water; 25, 50, 75 and 100% v/v ethanol were prepared as binder solutions. The addition of binder solution was slow and uniform over 3 min and mixing continued for a further 2 min. The wet mass was screened through a 1.6 mm aperture sieve and tray-dried overnight at 50°C. The dry granules were re-screened through a 1.6 mm aperture screen before blending in 0.5% magnesium stearate using a tumble mixer for 5 min. The level of salicylic acid produced by hydrolysis during wet massing and drying of each granulation was determined by the method of Tinker and McBay (1954).

(ii) Properties of binder solutions and solvents

(a) Solubility (C_s). The saturated solubility of acetylsalicylic acid in water; 25, 50, 75 and 100% v/v ethanol containing 6% w/w PVP was determined at 20°C. Saturated solutions were stored at 20°C with intermittent agitation for 48 h. They were filtered through a sintered glass 5/3 and immediately diluted using distilled water. The concentration was determined by UV spectrophotometry at about 275 nm using a Perkin Elmer Model 402 spectrophotometer with reference to a standard line. Acetylsalicylic acid in water obeyed the Beer-Lambert law in the range 0–250 $\mu g \cdot ml^{-1}$.

(b) Viscosity (η). The kinematic viscosity (cSt) of each binder solution containing 6% w/w PVP and when saturated with acetylsalicylic acid, and each solvent was determined using a suspended level viscometer at 20°C. These were converted to the coefficient of viscosity (cP) by dividing through by the solution or solvent density.

(c) Surface tension (γ). The surface tension (dyne $\cdot$ cm^{-1}) of each binder solution, and when saturated with drug, was determined at 20°C using a du Nuoy tensiometer fitted with a 4 cm platinum wire.

(d) Wettability ($r \cdot \cos\theta$). A lightly plugged, truncated section of a 10 ml burette was packed to a constant bulk density (0.568 g $\cdot$ ml^{-1}) with the ungranulated powder mix (90.9% acetylsalicylic acid and 9.1% Polyplasdone XL). 2 ml of binder solution was added onto the powder bed and the rate of fluid penetration (L) monitored with time (t). The (rate of penetration)^2 with time was linear for all systems, consistent with the Washburn equation (1921):

$$L^2 = (r \cdot \cos\theta) \cdot \frac{\gamma}{2\eta} \cdot t$$

where r is the average radius of the void spaces and θ is the contact angle.

By substituting in values for surface tension (γ) and viscosity (η), a wetting constant ($r \cdot \cos\theta$) could be determined for each binder solution and solvent.

(e) Volatility. The evaporation rate of each binder solution and solvent was determined at 50°C. A 20 g sample was pipetted into a petri dish (diameter 11 cm) and placed in the centre of a fan-convected oven (B.S. 2648; Gallenkamp, London). The percent weight loss cm^{-2} was determined over 30 min.

(iii) Properties of granules

(a) Sieve analysis. Sieve analysis was carried out on the powder blend and granules using DIN standard sieves vibrated on a Fritsch Analysette (Christeson: Gateshead) for 20 min. The cumulative % oversize was fitted to a log-probit plot using least-squares analysis. The degree of granulation could be estimated by determining the % of granules greater than the mean size of the original powder blend.

(b) Granule friability. Granule friability was evaluated by tumbling a 10 g sample of each granulation in a stainless steel cylinder of 3.8 cm diameter and 7.5 cm length, containing twenty 8 mm, 200 mg film-coated tablets of zero friability as ball-milling agents. The chamber was rotated 1000 times and a sieve analysis carried out on the resultant abraded granules (see iii (a)). The degree of friability could be estimated by determining the % of granules smaller than their original mean size prior to abrasion.

(c) Bulk density ρ_B. The bulk density of each granulation was determined in triplicate according to British Standard 1460 (1967).

(iv) Tablet properties

(a) Crushing strength (P). The mean of 10 tablets using a Schleuniger hardness tester (Zurich).

(b) Friability (F). The friability (% weight loss) of 5 tablets was assessed after 1000 revolutions at 75 rpm in stainless steel cylinders of 3.8 cm diameter and 7.5 cm length.

(c) Porosity. Tablet porosities were calculated from:

$$\text{Porosity } (\epsilon\%) = \left[1 - \frac{\text{Apparent Density}}{\text{True Density}}\right] \times 100$$

True density was determined by compressing granules to 10 tons on a hydraulic press. This mass corresponds to zero porosity and True Density = Weight of compact/volume.

The apparent density was determined similarly by dividing tablet weight by volume, calculated from tablet dimensions, measured using a micrometer.

Results and Discussion

(i) Properties of the granules

The solubility of acetylsalicylic acid in the aqueous and alcoholic binder solutions is shown in Table 1.

Hydrolysis occurred too rapidly in aqueous solvents at 50°C to allow solubility determinations at the drying temperature. The drug is poorly soluble in water (< 0.5%) but freely soluble in ethanol (13.3%). In the ethanol : water mixtures, a maximum occurs at about 80% v/v ethanol (Fig. 1). Such maxima exist in many mixed solvent systems (Lordi et al., 1964; Paruta and Irani, 1965) and are related to a specific dielectric requirement of the solute in the solvent (Paruta et al., 1962).

The levels of salicylic acid generated by hydrolysis during wet massing are shown in Table 2. Very little salicylic acid (< 0.25%) is generated by wet massing and drying at 50°C overnight. The highest level is generated by granulating with 50% ethanol since drug solubility is relatively high and there is sufficient water to promote hydrolysis. Water generates only 0.12% and this is limited by low drug solubility whereas at high alcohol content (> 75%), although drug solubility is high, less water is available to facilitate hydrolysis.

TABLE 1

ACETYLSALICYLIC ACID SOLUBILITY IN HYDROALCOHOLIC BINDER SOLUTIONS (CONTAINING 6% w/w PVP) AT 20°C

Solvent	Solubility (C_s mg·ml^{-1})
Water	4.66
25% ethanol	12.50
50%	79.00
75%	147.00
Ethanol	133.06

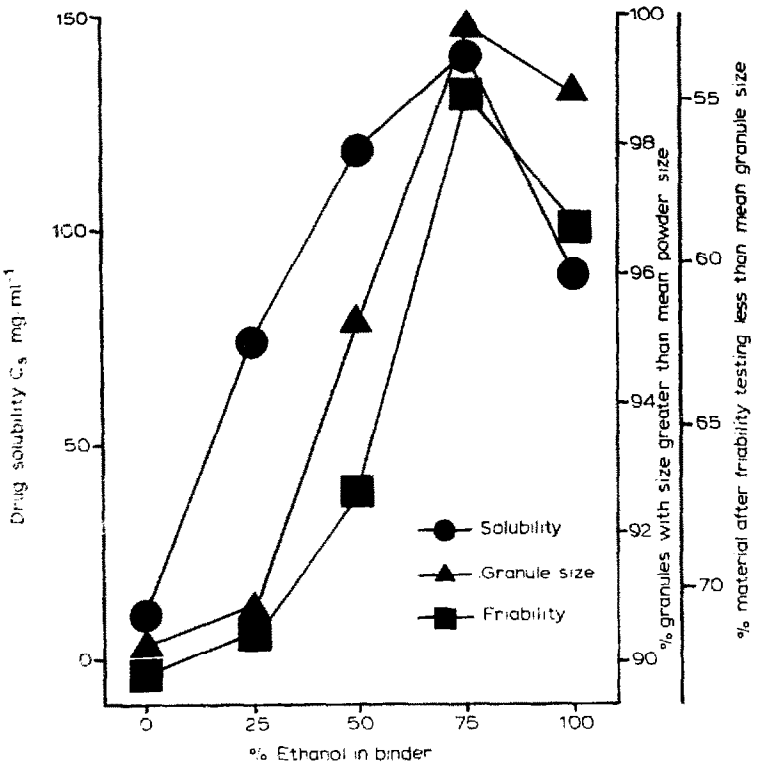

Fig. 1. Relationship between aspirin solubility in 6% w/w PVP solutions and granule size and friability.

The sieve analysis data for the granulations is shown in Table 3. All gave linear regressions ($P = < 0.001$) when plotted as cumulative % oversize on the probability scale against log sieve aperture size (Fig. 2).

The % granules with a size greater than the mean powder size could be obtained from the equation of the line (using least-squares analysis) and the extent of granulation embodied in this parameter is related directly to drug solubility (Fig. 1). A similar relationship does exist between mean granule size and solubility, but is not

TABLE 2

SALICYLIC ACID LEVELS IN ACETYLSALICYLIC ACID BEFORE AND AFTER WET MASSING AND DRYING AT 50°C

Granulation fluid	% Salicylic acid
Raw material	0.0108
Raw material after heating at 50°C overnight	0.0458
Water	0.1193
25% ethanol	0.1555
50%	0.2251
75%	0.2041
Ethanol	0.0823

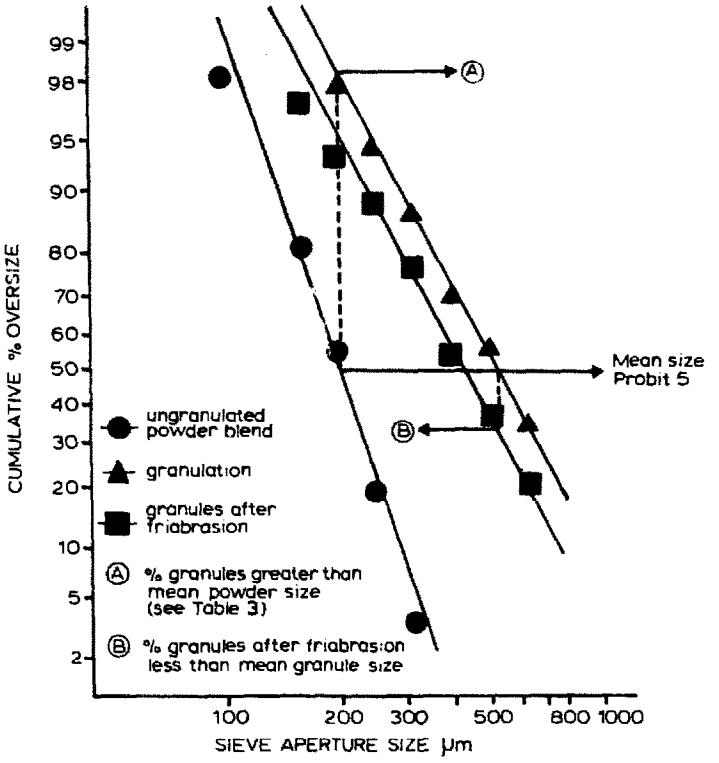

Fig. 2. Particle size distributions of powder blend, granulation and granules after abrasion (granulated using 6% PVP in 50% ethanol).

as sensitive, since it does not take the population distribution into account and screening through 1.6 mm (no. 10 mesh) prior to drying will also affect the effective granule growth that has occurred in the bowl.

Granule size distribution is defined by the standard deviation (σg) derived from

TABLE 3

GRANULE SIEVE ANALYSIS FROM LOG-PROBIT DATA

Granulation fluid	Mean sieve size (μm)	Standard deviation (σg)	r	% granules with size greater than mean powder size *
Ungranulated	201.33	1.331	0.9905	50.00
Water	454.91	1.855	0.9956	90.75
25% ethanol in water	521.97	1.783	0.9982	95.02
50% ethanol in water	531.60	1.612	0.9985	97.92
75% ethanol in water	592.30	1.537	0.9987	99.39
Ethanol	574.11	1.820	0.9992	95.99

* See Figure 2.

r = correlation coefficient.

the log-probit analysis and the uniformity of granule size is proportional to drug solubility. For example, the most uniform and therefore tightest distribution is obtained using 75% ethanol as binder vehicle, where drug solubility is highest; water produces granules with the widest distribution where drug solubility is extremely low. Increased solubility facilitates nucleation, and the dissolution of drug during massing produces viscous films which promote the adhesion of small particles onto larger granules. The combined effect leads to larger granules with a tight size distribution. Conversely, a poor solvent leads to poor wetting and granule growth is erratic. The resultant granules are small, with a wide distribution containing un-granulated powder.

As a consequence, increased drug solubility in the binder produces granules with reduced friability (Table 4). Granule abrasion resistance and strength will prevent poor handling characteristics which may result in impaired flow, with consequent tablet weight variation and inconsistent compression.

Several methods measuring breaking strength have been used (Harwood and Pilpel, 1968; Ganderton and Selkirk (1969); Gold et al., 1971), but give poor results due to the differences in granule size distribution and shape. Friability measurement (Fonner et al., 1966; Marks and Sciarra, 1968; Hunter, 1973) using a single sieve before and after abrasion is only valid for comparing granules of the same size. More recently, Rubinstein and Musikabhumma (1978) put forward a friability index from the quotient of the mass median diameter before and after abrasion, in an attempt to compare different sized granules. However, none of these methods are sensitive or take the generated distribution into account. In the present work, the sieve analysis of the granules after abrasion has been fitted by log-probit analysis and the degree of friability measured as the % of material after friability testing less than the mean granule size (Fig. 2). This parameter (Table 4) analogous to that used in evaluating granulation (Table 3), takes the initial and final size and distribution into account. The relationship between friability and solubility is shown in Fig. 1.

It is clear therefore that drug solubility contributes significantly to granule growth, size and distribution and significantly reduces granule friability. This presumably occurs by secondary binding due to recrystallization of dissolved drug.

TABLE 4

GRANULE FRIABILITY MEASUREMENTS

Granulation fluid	Mean sieve size (μM)		% decrease after friability testing	% material after friability test less than mean granule size
	Before	After friability testing		
Water	454.9	320.7	29.51	72.75
25% ethanol in water	522.0	372.1	28.72	71.40
50% ethanol in water	531.0	434.8	18.20	67.01
75% ethanol in water	592.3	539.3	8.96	54.71
Ethanol	574.1	497.4	13.36	58.81

TABLE 5

PROPERTIES OF BINDER SOLUTIONS CONTAINING 6% w/w POLYVINYLPYRROLIDONE

Binder vehicle	Viscosity (cP)	Surface tension (dynes·cm^{-1})	Penetration rate $K \times 10^{-2}$ cm^2·s^{-1}	Wettability r·cos $\theta \times 10^{-4}$
Water	67.15 (51.64) *	69.51(51.25) *	2.05	4.100
25% ethanol	194.83(166.30)	42.63(39.53)	1.33	12.157
50% ethanol	287.42(260 14)	33.59(31.32)	0.93	15.915
75% ethanol	240.72(246.39)	30.14(28.44)	1.17	18.689
Ethanol	186.37(174.02)	26.35(23.89)	1.16	16.410

* Values in parentheses represent drug-saturated binder solution.

(ii) Properties of the binder solution

There are other consequences of changing the binder vehicle, which result in differences in the behaviour of the binder solution (Table 5).

In aqueous ethanol mixtures, maximum binder viscosity occurs at 50% ethanol. Binder viscosity does not therefore appear to control the granulation process

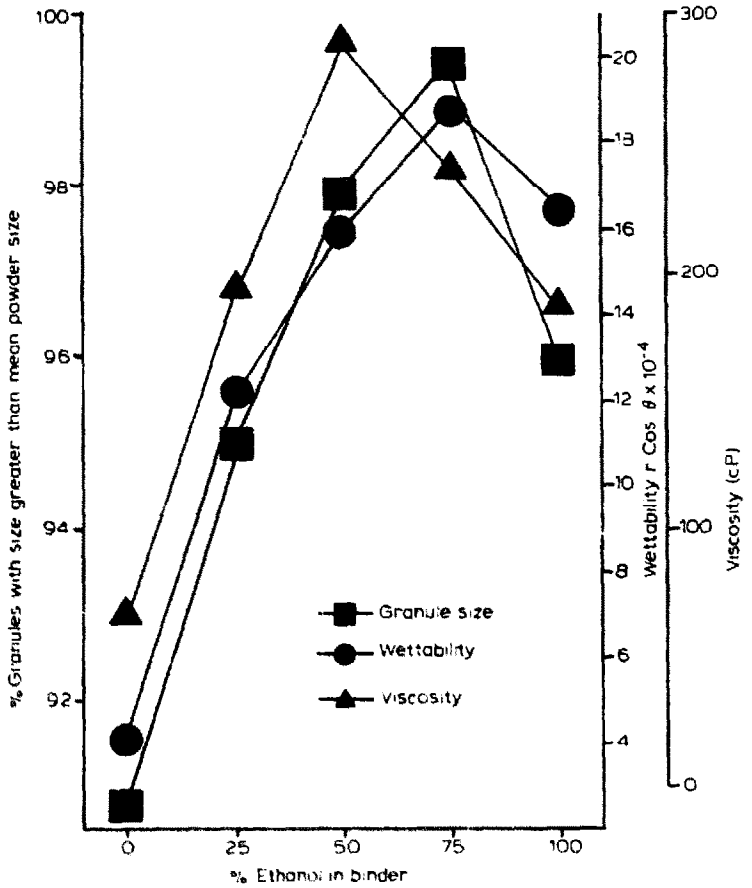

Fig. 3. The relationship between granule size and binder viscosity and wettability.

(Fig. 3). Viscosity, however, would be a controlling factor if the binder used is extremely viscous and difficult to disperse and then in situ activation is necessary. Generally, saturation of the binder with drug causes a small decrease in viscosity, since the drug is competing for the solvent. Where an increase occurs, with 75% ethanol, the high drug content will increase the binder viscosity. Wettability is, however, clearly important, with a direct relationship between granule size and $r \cdot \cos \theta$ (Fig. 4). Similar relationships have been reported by Aulton et al. (1977) and Aulton and Banks (1979), who used contact angle measurements. In the present work, the measurement of penetration rates through a packed column and the application of the Washburn equation (1921) is directly analogous to the addition of binder in the planetary mixer during wet massing and is therefore the method of choice. While changes in binder vehicle affect wettability, the addition of surface-active agents or more hydrophilic excipients will similarly increase wetting and presumably will also promote granule growth and size.

Binder surface tension decreases with increasing alcohol content and is marginally

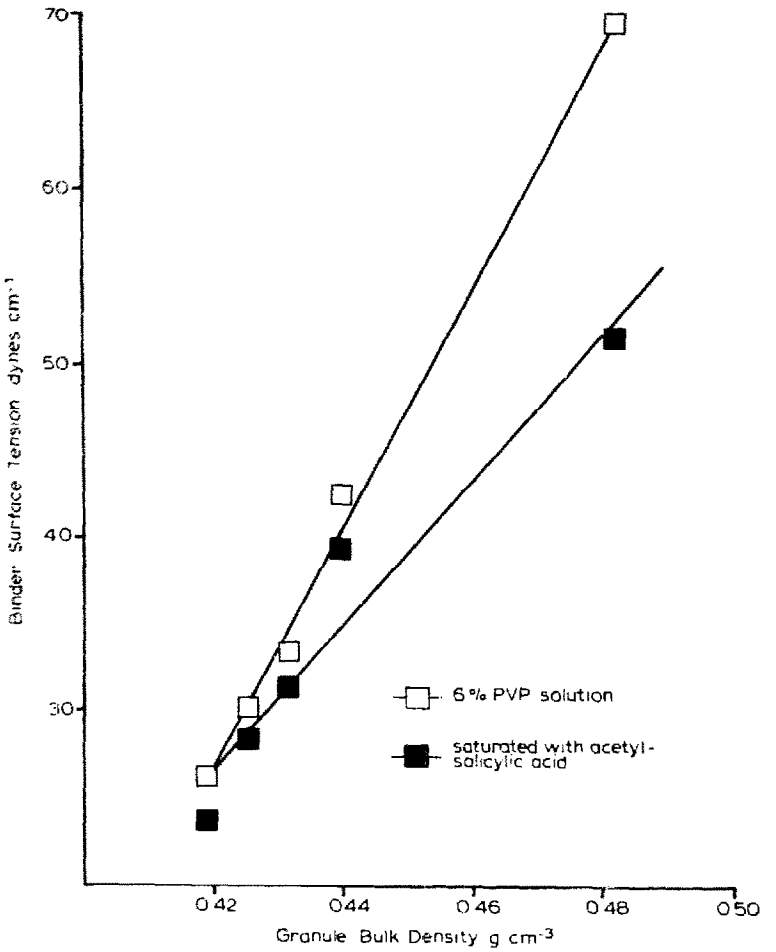

Fig. 4. Relationship between granule bulk density and binder solution surface tension.

reduced by dissolved drug. A linear relationship exists between surface tension and granule bulk density (Fig. 4). The two linear regressions show the difference in surface tension for pure PVP solutions and those saturated with drug. During the course of granulation and drying, the surface tension would exist somewhere between the two extremes. During the initial phases of granulation the surface tension would be near to values for pure PVP solutions. At the end of granulation and during drying the surface tension would be that of the saturated solutions of drug in PVP. The linear relationship between surface tension implies that the addition of surface-active agents to binder solutions, commonly employed to improve subsequent wetting during disintegration and dissolution of the compressed tablets, may also decrease bulk density. This will increase porosity and reduce granule compactness and affect compressibility.

After initial wetting during wet massing, agglomeration produces the pendular state; further binder addition displaces air and the funicular state is obtained; continued massing produces the capillary state. The tensile strength of the liquid films formed are described by equations (Barlow, 1968) which show that the strength of the funicular and pendular bonds are dependent upon binder surface tension. Only at the capillary stage does the contact angle, i.e. wettability become important. Surface tension is measured at the air–liquid interface whereas the contact angle measures spreadability at the liquid–solid interface. Thus throughout the massing process, the surface tension of the binder film has a direct bearing upon the tensile strength of the lenticular films produced. This surface tension will determine how

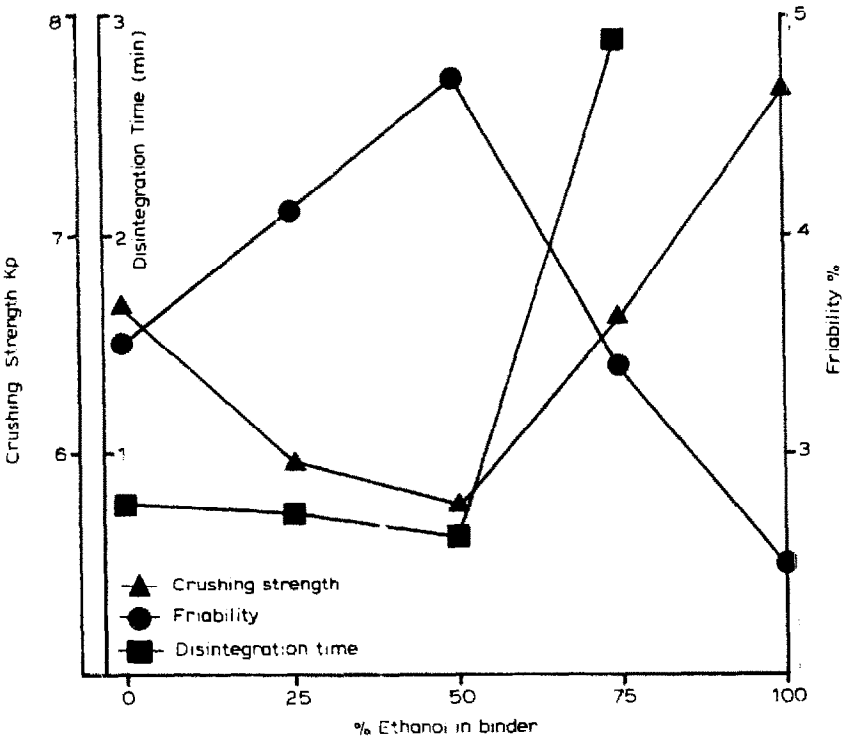

Fig. 5. Tablet properties of acetylsalicylic acid granulated with PVP in alcohol:water mixtures.

close discrete particles are drawn together during wet massing and therefore accounts for the direct relationship between granule bulk density and surface tension.

In summary, solubility and wettability determine the degree of agglomeration occurring during wet massing (Figs. 2 and 4). Viscosity has a smaller effect. Surface tension, on the other hand, determines the tensile strength of the lenticular films formed during wet massing and controls the bulk density of the granules (Fig. 5).

(iii) Tablet properties

The properties of the tablets compressed at 150, 225 and 300 $MN \cdot m^{-2}$ are shown in Table 6. Many of the profound differences in granule properties (part (i)) due to the binder solution (part (ii)) are largely obscured after compression. However, some trends emerge.

Up to 75% ethanol in the binder vehicle produces tablets which increase in crushing strength with compression pressure indicating no tendency to cap or laminate. However, pure alcohol produces tablets where increased compaction pressure results in a reduction in strength indicated by incipient capping during hardness testing. Differences in porosity are small. The crushing strengths are minimum with 50% ethanol. Although little recrystallization occurs with water, the tablets are stronger, probably because aspirin bonds by fragmentation, and a reduced granule strength yields better consolidation upon compression. Further-

TABLE 6

PHYSICAL PROPERTIES OF ACETYLSALICYLIC ACID TABLETS PREPARED FROM GRANULES USING DIFFERENT BINDER VEHICLES

Granulating fluid	Compression force ($MN \cdot m^{-2}$)	Crushing strength (Kp)	Friability (%)	Porosity (%)	Disintegration time B.P. (1973)
Water	150	5.64 (10.9)	4.7	44.56	0.70
	225	6.68 (8.3)	3.5	44.17	0.77
	300	7.14 (6.8)	3.4	43.37	0.93
25% Ethanol	150	5.72 (7.3)	4.4	44.05	0.72
	225	5.96 (5.4)	4.1	43.55	0.73
	300	6.36 (9.6)	3.7	43.26	0.90
50% Ethanol	150	5.44 (6.8)	4.8	44.54	0.60
	225	5.76 (4.4)	4.7	44.33	0.62
	300	6.77 (7.2)	2.7	44.23	0.98
75% Ethanol	150	6.60 (8.4)	3.0	44.98	5.12
	225	6.62 (5.6)	3.4	44.63	[illegible]
	300	7.36 (4.5)	3.1	44.37	8.42
Ethanol	150	7.65 (8.6)	2.4	44.97	» 15
	225	7.66 (5.8)	2.5	45.12	» 15
	300	7.56 * (7.0)	2.9	45.33	» 15

Parentheses give coefficient of variation (%)

* Tablets capped during test

» Did not disintegrate at all.

TABLE 7

BINDER SOLUTION AND SOLVENT EVAPORATION RATES AT 50°C

Solvent	Evaporation rate (% weight loss) ($cm^{-2} \cdot min^{-1}$)	
	Binder solution	Solvent
Water	14.57	14.22
25% ethanol	22.65	25.70
50% ethanol	32.57	38.04
75% ethanol	40.14	44.68
Ethanol	43.41	58.57

more, smaller granules generally produce harder tablets due to a greater available bonding surface, if the bonding mechanism is fragmentation. However, after granulation with 75% ethanol and pure alcohol, the tablets are harder, presumably due to the increased solute deposition and granule hardness.

There is a corresponding reduction in friability, and irrespective of which binder solution was used in wet massing, a simple linear relationship exists between crushing strength (P) and friability (F): $F = 10.075 - 0.9897P$; $r = 0.9285$; ($P = < 0.001$).

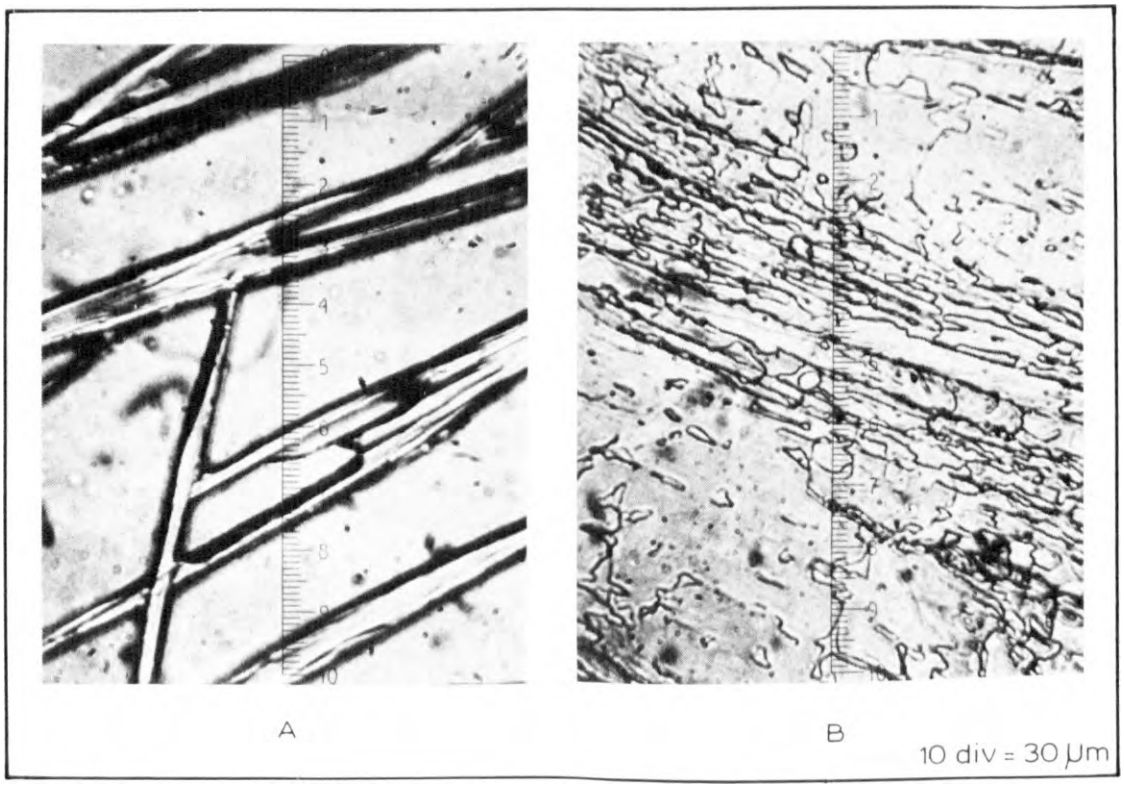

Fig. 6. Aspirin recrystallized from water (A) and ethanol (B).

Thus although secondary binding reduces granule friability (Fig. 1), it does not improve tablet friability fundamentally, which is simply dependent upon the mechanical strength of the tablets.

All aqueous alcoholic massed granules produced tablets which disintegrated (Fig. 5). However, pure alcohol prevented any disintegration. The reason for this behaviour depends to a large extent upon binder solvent volatility (Table 7).

Where volatility is low, so is the corresponding drug solubility, and this leads to little solute deposition and the generation of relatively large crystals (Fig. 6). Where volatility is high, e.g. pure alcohol, considerable solute deposition occurs and the crystals produced are small (Fig. 6). Cross-linked PVP (PVP-XL) acts as a tablet disintegrant by both capillary and swelling activity (Kornblum and Stoopak, 1973). If the fine drug crystals are redeposited around the PVP-XL particles during drying or the drug-saturated binder solution is drawn into the disintegrant particles during wet massing where the drugs crystals are then deposited, this combined effect will prevent penetration of fluid and impair the swelling potential of the disintegrant.

Conclusion

In conclusion, profound differences in granule properties occur when the binder solvent is changed. Greater solubility of the drug produces granules whose size is increased, distribution tightened, and whose friability is decreased. Greater wettability improves granule growth whereas binder viscosity is not fundamentally important. The surface tension of the binder controls granule bulk density.

The friability of the tablets is not reduced by the secondary binding caused by solute deposition but is related to tablet strength. Higher drug solubility in the binder produces tablets with impaired disintegration and is related to solvent volatility and the deposition of fine crystals blocking the capillary network.

References

Aulton, M.E., Banks, M. and Smith, D.K., The wettability of powders during fluidised bed granulation. J. Pharm. Pharmacol., 29 Suppl. (1977) 59P.

Aulton, M.E. and Banks, M., Influence of hydrophobicity of the powder mix on fluidised bed granulation. Proc. 2nd Int. Conf. Powder Technol., Basel, 1979.

Barlow, C.G., Aggregation, the manufacture of granules, pellets and tablets: the granulation of powders. Chem. Eng., July/Aug. (1968) CE196–201.

British Standard 1460, Method for determination of apparent density after compaction of precipitated calcium carbonate, 1967.

Capes, C.E. and Danckwerts, P.V., Granule formation by the agglomeration of damp powders. Trans. Instn. Chem. Engrs., 43 (1965) T116–125.

Fonner, D.E., Banker, G.S. and Swarbrick, J., Micromerities of granular pharmaceutical solids I: Physical properties of particles prepared by five different granulation methods. J. Pharm. Sci., 55 (1966) 181–186.

Ganderton, D. and Selkirk, A.B., The effect of granule properties on the pore structure of tablets of sucrose and lactose. J. Pharm. Pharmacol., 22 (1970) 345–353.

Ganderton, D. and Hunter, B.M., Comparison of granules prepared by pan granulation and by massing and screening, J. Pharm. Pharmac., 23 Suppl. (1971) 1S–10S.

Gold, G., Duvall, R.N., Palermo, B.T. and Hurtle, R.L., Granule strength as a formulation factor I: Instrumentation. J. Pharm. Sci., 60 (1971) 922–925.

Harwood, A.F. and Pilpel, N., Granulation of griseofulvin. J. Pharm. Sci., 57 (1968) 478–481.

Healey, J.N.C., A study of the effects of binding agents upon some tablet and granule properties. Ph.D. thesis, Liverpool Polytechnic, 1976.

Hunter, B.M., A friability test for granules. J. Pharm. Pharmacol., 25 Suppl. (1973) 111P.

Kapur, P.C. and Fuerstenau, D.W., Size distributions and kinetic relations in the nuclei region of wet pelletization, Ind. Eng. Chem. (Proc. Des. Dev.), 5 (1966) 5–10.

Kornblum, S.S. and Stoopak, S.B., A new tablet disintegrating agent: cross-linked polyvinylpyrrolidone. J. Pharm. Sci., 62 (1973) 43–49.

Lordi, N.G., Sciarrone, B.J., Ambrosio, T.J. and Paruta, A.N., Dielectric constants and solubility. J. Pharm. Sci., 53 (1964) 463–464.

Marks, A.M. and Sciarra, J.J., Effect of size on other physical properties of granules and their corresponding tablets. J. Pharm. Sci., 57 (1968) 497–504.

Maudling, H.V., Zoglio, M.A. and Johnston, E.J., Pharmaceutical heterogeneous systems II: Study of hydrolysis of aspirin in combination with fatty acid lubricants. J. Pharm. Sci., 57 (1968) 1873–1877.

Newitt, D.M. and Conway-Jones, J.M., A contribution to the theory and practice of granulation. Trans. Instn. Chem. Engrs., 36 (1958) 422–442.

Paruta, A.N., Sciarrone, B.J. and Lordi, N.G., Correlation between solubility parameters and dielectric constants. J. Pharm. Sci., 51 (1962) 704–705.

Paruta, A.N. and Irani, S.A., Dielectric solubility profiles in dioxane–water mixtures for several antipyretics: effect of substituents. J. Pharm. Sci., 54 (1965) 1334–1338.

Pietsch, W., Strength of agglomerates bound by salt bridges. Can. J. Chem. Eng., 47 (1969) 403–409.

Rubinstein, M.H. and Musikabhumma, P., A universal friability test for tablet granules. Pharm. Acta Helv., 53 (1978) 125–129.

Rumpf, H., Basic principles and methods of granulation. Chem. Ing. Tech., 30 (1958) 144–158.

Seager, H., Burt, J., Ryder, J., Rue, P.J., Murray, S., Beal, N.K. and Warrack, J.R., The relationship between granule structure, process of manufacture and the tableting properties of a granulated product Part I: Granule structure. Int. J. Pharm. Tech. Prd. Mfr., 1 (1979) 36–44.

Tinker, R.B. and McBay, A.J., Spectrophotometric determination of acetylsalicylic and salicylic acids. J. Am. Pharm. Ass. Sci. Edn., 43 (1954) 315–318.

Washburn, E.H., The dynamics of capillary flow. Phys. Rev., 17 (1921) 273–283.