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Agglomeration state and migration of drugs in wet granulations during drying

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Abstract

Migration of drugs was studied during drying of wet granules, agglomerated at pendular and funicular state (S_3 and S_4). Granulating liquids of different viscosity (2.5 and 7.5 mPa s) and drugs and diluents of different solubility and wettability were employed and correlation was sought between distribution of the liquid, wet kneading parameters (torque and liquid consumption S%), solid–liquid interactions (work of adhesion and spreading coefficients) and the migration of drugs. It was found that drug migration, expressed as CV% of its content, was strongly dependent on the type of diluent. Also, the type of diluent exerted the strongest effect on torque and liquid consumption during wet kneading and a significant one on moisture content of the final granulations. Viscosity of the granulating liquid and molecular weight of the binder had no effect on liquid consumption but viscosity had a significant one on drug migration. Significant linear relationships were found between spreading coefficients and the liquid consumption (S%) at the mid-state of funicular agglomeration $(S_3 + S_4)/2$ or the torque at the capillary state S_5. Migration of drug was remarkably lower for drying in the microwave oven and increased from the pendular (S_3) to the funicular (S_4) agglomeration state when drying in conventional oven was applied. Linear relationships were found between migration (CV%) and the spreading coefficient of liquid on solid, λ_{LS}, for the low and the high viscosity levels of the granulating liquid, with $r = 0.965$, $P = 0.05$ and $r = 0.901$, $P = 0.10$, respectively. Also, a general linear relationship ($r = 0.903$ and $P = 0.002$) accommodating all experimental data was found between migration (CV%) and the ratio λ_{LS}/viscosity. Drug migration increases with solubility and may become a problem in a range higher than 1 g in 148–400 ml of granulating liquid.

Keywords: Agglomeration state; Torque; Liquid consumption; Spreading coefficients; Type of diluent; Viscosity of granulating liquid; Drying

1. Introduction

In addition to the liquid distribution, the dissolving ability of the granulating liquid may alter the partitioning of active ingredients between the liquid and the solid excipients of a formulation. Besides, the solid–liquid interactions, such as wet-

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ting, spreading, and swelling, also affect the quantity of liquid required for optimal granule formation and its distribution in wet agglomerates (Buckton 1990; Malamataris and Kiortsis 1997). Therefore, during the drying of wet granules the migration of both liquid and drug is expected to be greatly affected and consequently the content uniformity of the final dosage forms (tablets or capsules).

Literature survey on the subject shows that until now the effect of the distribution of the granulating liquid and of it's alteration due to formulation variables on the migration of drugs during the drying of wet granulations, has not been evaluated, although, its importance was pointed. Chaudry and King (1972) found that the use of acacia as binder impedes migration of sodium warfarin. Travers (1975) investigated the effect of the method of drying on the migration of sodium chloride in kaolin granules, and found that it was greater for infrared radiation, less for hot air circulation and negligible for microwave and vacuum drying. Warren and Price (1977a,b) examined the effect of particle size of lactose as diluent, of drying temperature and of the viscosity of PVP solution used as binder. They found that migration increased with decreasing particle size due to smaller size of capillaries and larger intergranular contact, but decreased with the viscosity of binder solution and was not affected by the drying temperature in the range 40–80 °C. Kiekens et al. (1999, 2000) confirmed the above results on the drying method and temperature. They further suggested the use of binder solution as a means for preventing migration of riboflavin, and specified a minimal viscosity of 100 mPa s. Ojile et al. (1980) found that closer packing of granules results in higher migration due to the smaller size of capillaries and that higher moisture content also results in higher migration due to the increased ability of transport to the surface. Boroujerdi (1984) developed a model describing the transport of active ingredients (drugs) in a wet granulation bed. It takes into account the packing (porosity or volume fraction of air), the volume fraction and the properties of granulating liquid, such as surface tension, viscosity and solubility of active ingredient or the partition between liquid and solid components (diluents). But, no experimental evidence supported the theoretical derivation of the model.

The distribution of a granulating liquid in wet granules can be characterized qualitatively by the agglomeration state (pendular, funicular or capillary). It can be expressed quantitatively by the total porosity and the proportion of liquid and solid components, or by the volume of the liquid divided by the total volume of solid plus liquid, expressed as percentage, $S\%$ (Hancock et al., 1994). Agglomeration state can be identified from overwetting tests, by recording the resistance to mixing either as torque or as electric power consumption (Bier et al., 1979). Therefore, it was thought of interest to examine the migration of drugs during drying of wet granules, agglomerated at the pendular and funicular agglomeration states (S_3 and S_4) which are giving optimal pharmaceutical granules, by employing granulating liquids of different viscosity and drugs and diluents of different solubility and wettability.

Such examination would allow seeing if there is any correlation between the distribution of granulating liquid, the wet agglomeration parameters (torque and liquid consumption), the solid–liquid interactions (work of adhesion and spreading coefficients) and the migration of drugs in dried wet granulations.

2. Materials and methods

2.1. Materials

The materials were: alpha lactose monohydrate (DMV, Veghel, The Netherlands), maize starch (Cerestar, Milano, Italy) and dicalcium phosphate dihydrate USP (Rhône–Poulenc, Cranbury, NJ, USA) as diluents; prednisolone (Nycomed, AS Oslo, Norway), propranolol hydrochloride BP (Zeneca, England) and salicylic acid (Rhône–Poulenc, Cranbury, NJ, USA) as active ingredients; PVP K15 and K30 (Fluka Chemie GmbH, Buchs, Switzerland) as granulating binders and distilled water as granulating liquid.

2.2. Characterization of materials

Viscosity, surface tension (γ_L) and density of aqueous PVP solutions, as well as their dissolving ability for the drugs were measured by using presaturated granulating liquids with the diluents employed. Contact angle (θ) with the powdered diluents and work of adhesion [$W_a = \gamma_L(1 + \cos\theta)$] as well as spreading coefficients ($\lambda_{LS} = W_a - 2\gamma_L$ and $\lambda_{SL} = W_a - 2\gamma_S$) were determined. Work of adhesion (W_a) and spreading coefficients (λ_{LS} and λ_{SL}) were also determined from the dispersion and polar components of the surface free energies of the diluents (γ_S^d and γ_S^p) and of the granulating solutions saturated with diluent (γ_L^d and γ_L^p). For their determination distilled water and methylene iodide (Aldrich-Chemie, Germany) were used as the reference liquids and parafilm (American Can Company, Neenach, USA) as the reference solid (Zografi and Tam, 1976; Malamataris and Pilpel, 1982; Buckton and Newton, 1986) by applying the Wu equation (Wu and Brzozowski, 1971):

$$Wa = 4\left[\frac{\gamma_S^d \gamma_L^d}{\gamma_S^d + \gamma_L^d} + \frac{\gamma_S^p \gamma_L^p}{\gamma_S^p + \gamma_L^p}\right] \quad (1)$$

The concentration of granulating liquids in PVP of different molecular weight was selected on the basis of viscosity plots, presented in Fig. 1. It was for K15 10 and 24% w/v and for K30 5 and 12% w/v corresponding to 2.5 and 7.5 mPa s viscosity. Contact angle (θ), was determined by measuring the maximum height of a drop on compacts, 5 cm in diameter and about 0.5 cm in height (Kossen and Heertjes, 1965). Density of liquids was measured by the gravimetric bottle method and surface tension (γ_L) was determined by using a Du Noüy tensiometer (Krüss 13337, Hamburg, Germany). Viscosity was measured with a glass capillary (Ostwald) viscometer and equilibrium solubility of the drugs was determined in both water and granulating solution, by dispersing excess amount of drug in the liquid and measuring the concentration after equilibration. The apparent particle density of dry powders and of wet granules was measured on an air comparison pycnometer (Beckman, Model 930). In the case of wet granules, measurement started immediately after locking the sample in place, in order to avoid evaporation, as described in the manufacturer's manual. The bulk density of the dry powdered diluents was determined from the weight and volume after pouring 110 g in a 250 ml volumetric cylinder, as described in the British Standards 1640 (1967). Three replications were made for each determination of all the above-mentioned properties and the mean value was calculated.

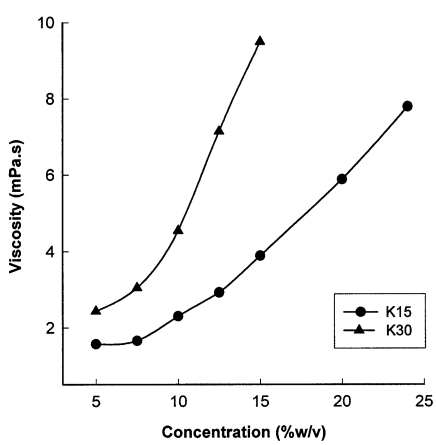

Fig. 1. Plots of viscosity versus concentration for aqueous solutions of PVP with different molecular weight (K15, K30).

Particle size range, d_{10}–d_{90}, of the diluents and mean particle roundness (Hausner 1966), were determined using an image processing and analysis system (Quantimet 500, Leica, Cambridge, UK), by examining about 500 particles, in 3–4 different optical fields, after dispersion in liquid paraffin oil.

2.3. Overwetting tests

Mixing of diluents with PVP solutions corresponding to viscosity of 2.5 and 7.5 mPa s was performed. A specially constructed wet-kneading rheometer (shear mixing and massing apparatus) was used for measuring both the electric power consumption and the torque exerted on the mixing vessel. A peristaltic-tube-pump was employed for the continuous addition of granulating liquid at constant rate in order to have information about the agglomeration process until overwetting (quick dropping of mixing resistance).

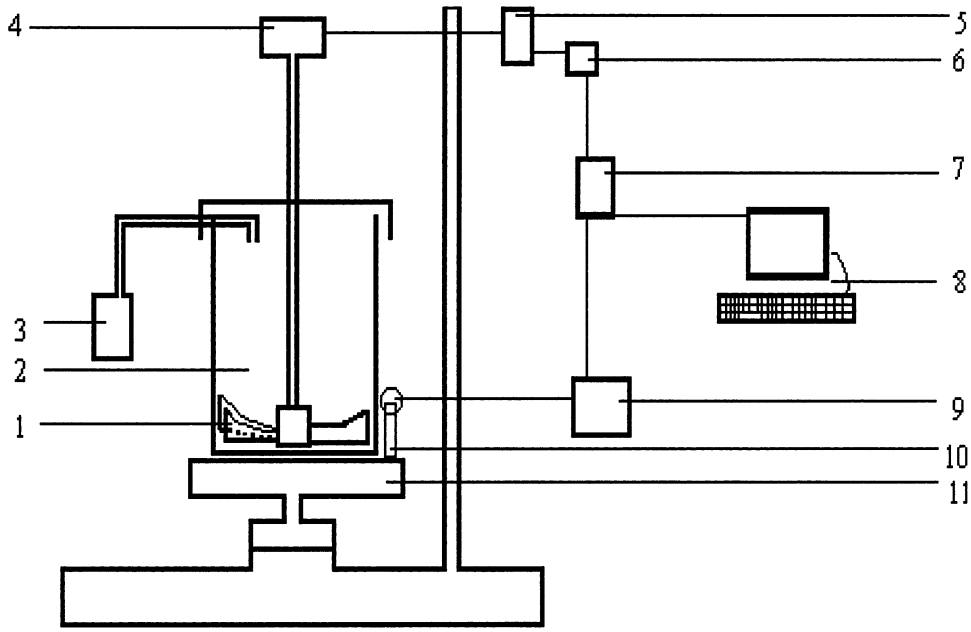

Fig. 2. Diagram of the wet-kneading rheometer. (1) three-blade impeller, (2) 1 l mixing vessel, (3) peristaltic-tube pump, (4) stirrer, (5) stirring speed controller, (6) current to voltage transformer, (7) electronic polymeter, (8) computer, (9) amplifier, (10) load cell, (11) rotating platform.

The wet-kneading rheometer, shown schematically in Fig. 2, consisted of a three-blade impeller placed centrally in a 1 l cylindrical vessel and is a modification of that reported earlier (Malamataris and Kiortsis, 1997). The impeller was fitted on a stirrer (IKA-RE 162, Staufen, Germany) which provided the electrical current (A) required to maintain a constant stirring rate (200 rpm), through a current to voltage transformer and a linear rectification unit. The mixing vessel was mounted on a rotating platform linked tangentially to a dynamometer (50 N load cell with amplifier, type E 308, RDP Electronics, UK). The signals from the dynamometer and the stirrer were transferred through an electronic polymeter (Handyscope, type TP208-12 bits-20 MHz, Tie Pie Engineering, The Netherlands) to a computer equipped with the necessary software programs for the capture and analysis of data in digital form. From every granulation process more than 300 points (1 point every 2 s) were collected and graphs of torque and electric power consumption versus quantity of added liquid were plotted. They were always proportional. Therefore, only torque will be considered in this investigation.

Before starting each mixing, a steady baseline of torque value was obtained from the empty mixer over a short period of 30 s, which was taken as zero point. Then, certain quantity of diluent corresponding to about 500 ml of bulk powder was added to the mixing bowl after sieving to destroy the lumps. It was selected as equivalent to 50% of the vessel volume, sufficient to cover the mixing blades at all times. The diluent was dry-mixed in the rheometer for 1 min, using speed of 200 rpm and the torque exerted was recorded. Then, liquid was added slowly and continuously with the mixer motor running until a rapid reduction of the torque was observed due to overwetting of the powder substrate.

All the overwetting tests were performed in triplicate. From the single event profiles of torque versus granulating liquid addition (Fig. 3) the characteristic agglomeration states were established and the quantities of granulation liquid corresponding to the boundaries of these states

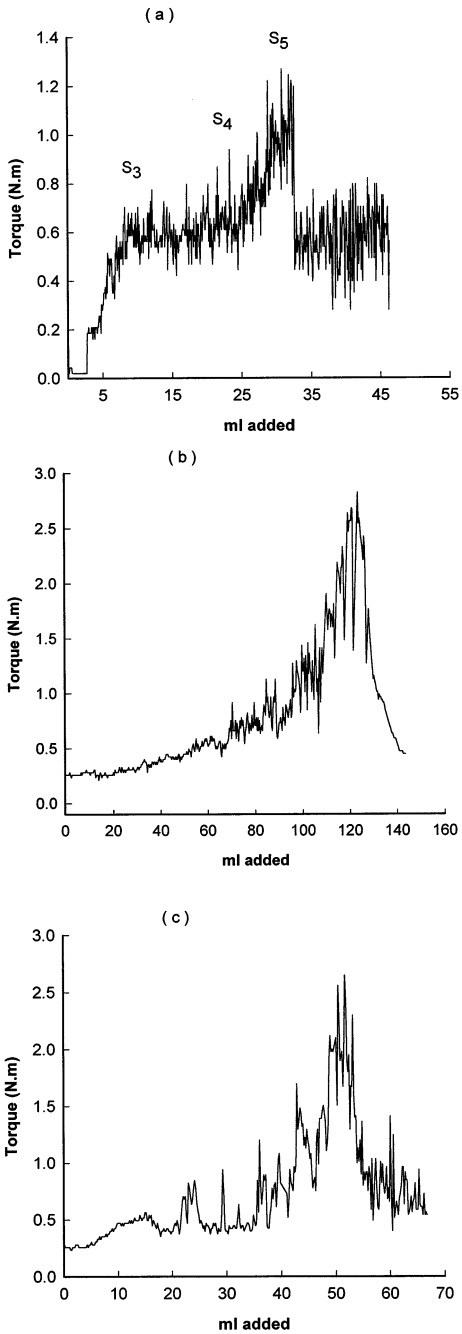

Fig. 3. Typical profiles of torque exerted on the mixing vessel during the overwetting tests of lactose (a), starch (b) and dicalcium phosphate dihydrate (c) with aqueous PVP granulating solution K30-5% w/v of 2.5 mPa s.

(S_3, S_4 and S_5, Fig. 3) were determined. This was done by first applying the technique of locally weighted regression (SigmaPlot 5.0, Chicago, USA) to obtain a smooth curve through the data (smoothing factor = 0.2) and subsequently determining the intersection of the tangents corresponding to the different states (Bier et al., 1979).

2.4. Wet agglomeration at certain states

Further wet-kneading experiments were performed by adding selected amounts of granulating liquids in 1.0% w/w dry mixtures of drugs in the diluents, obtained by applying initially a dilution procedure (geometric mixing) and then by physical mixing for 15 min in a turbula mixer (W.A. Bachofen, Switzerland) at 45 rpm. The amounts of granulating liquids employed correspond to the boundaries and the middle of agglomeration states S_3 and S_4. The rate of liquid addition was varied depending on the total amount of liquid added, in order to achieve about 10 min duration of the granulation. Massing was applied for about 2.5 min after the end of the liquid addition. Then, the wet granulated mass was passed through a 2 mm sieve, placed in drying-cell and dried at 60 °C to constant weight. The drying-cell was made of acrylic plastic and consisted of five layers, as described by Warren and Price (1977a). An additional single layer drying-cell was used as control. Two drying methods were employed, in a conventional laboratory air-circulation oven (model UT6, Heraeus Instruments GmbH Hanau, Germany) and in a microwave oven (model RS591B, Amana Iowa, USA), equipped with a temperature sensor for maintaining the temperature inside the drying granules constant. The drying time varied from 3 to 6 h in the conventional oven and from 0.5 to 1.5 h in the microwave oven, depending on the granulated diluent.

2.5. Sampling procedure and drug assay

Drug content was determined in the 1% w/w dry physical mixtures and in their wet granulated masses before placing in the drying-cells, by taking four random samples (approximately 0.5 g each). The coefficient of drug content variation

Table 1
Physical properties of diluents

Diluent	Particle size range d_{10}–d_{90} (μm)	Roundness	Density (g cm^{-3})		Dry mixing resistance (N m) × 10^3	Components of surface free energy (mN m^{-1})		
			Apparent particle	Bulk		γ_S^d	γ_S^p	γ_S
Lactose	8–30	1.62	1.52	0.54	7.0	37.4	35.0	72.4
Starch	11–25	1.46	1.48	0.52	2.0	38.3	27.0	65.3
DPD	18–42	1.89	2.45	0.57	3.0	32.0	37.4	69.4

γ_S^d, dispersion; γ_S^p, polar; γ_S, total surface free energy.

was $< 2\%$. Also, the granules placed in the five-layer drying-cell and in the control single-layer drying-cell were sampled after their drying. Samples of about 0.1 g were taken from five different points of each layer, combined and assayed for drug content spectrophotometrically.

Accurately weighed portions (0.5 g) of combined samples were dissolved in 10 ml of 0.1 N HCl, for the case of propranolol hydrochloride granules, in 10 ml of methanol, for the case of prednisolone and in 10 ml of water/ethanol (1:1 w/w), for the case of salicylic acid. Absorbance was measured at 286, 244 and at 305 nm, respectively. Diluents and PVP did not interfere with the assay at these wavelengths. The coefficient of variation of drug content (CV%) determined in the five layers of drying cell compared with the drug content in the single-layer cell was used as an indication of the extent of drug migration in the dried granulations.

All statistical analyses of the experimental data were made using SPSS 9.0 statistical software (SPSS Inc Chicago, IL, USA).

3. Results and discussion

3.1. Liquid–solid interactions and overwetting testing

In Table 1 are given the physical properties of the diluents. Their particle size is similar and roundness is lowest or sphericity is highest for the starch particles. Bulk and apparent particle densities of lactose and starch are very close and those of dicalcium phosphate dihydrate are larger. The resistance to dry mixing, in the case of lactose, is more than twice larger than those for the other two diluents. The lowest mixing resistance corresponds to the most round starch particles and the highest to lactose with the highest proportion of fine particles. From Table 1, it is also seen that the surface free energy of the diluents decreases in the order lactose > dicalcium phosphate dihydrate > starch, which is the same as in mixing resistance.

Table 2 summarizes the results of contact angle for the saturated granulating solutions with parafilm, of density and of polar and non-polar components of their surface tension. It can be seen that the value of the surface tension increases in the order lactose < dicalcium phosphate dihydrate < starch and for the K30 5% w/v granulating liquid it is similar (59 mN m^{-1}) for starch and dicalcium phosphate. The lowest surface tension of lactose should be related to its higher solubility in the aqueous PVP solutions as it is also indicated from the density values shown in Table 2.

Table 3 lists numerical values of contact angle (θ) for the saturated aqueous PVP granulating solutions with the three diluents employed, together with the work of adhesion and spreading coefficients. They were derived from dispersion and polar components of surface energy, W_{a1}, λ_{LS1} and λ_{SL1}, as well as from surface tension and contact angle of granulating liquid and diluent, W_{a2}, λ_{LS2} and λ_{SL2}. It can be seen that the values of contact angle (θ) increase for the three diluents in the order lactose < dicalcium phosphate dihydrate < starch, which is similar to that of surface

tension. From Table 3 also it can be seen that W_{a2}, λ_{LS2} and λ_{SL2} have lower values than W_{a1}, λ_{LS1} and λ_{SL1}, respectively. The spreading coefficient of the granulating liquids on the diluents, λ_{LS1} varies from -10.9 to $+10.5$ mN m^{-1}, showing that spreading will be favored to a different degree.

For optimum spreading and formation of a strongly adhering film, λ_{LS1} should be positive and earlier work (Rowe, 1989) has shown that this holds true for diluents with fractional polarity $(=\gamma_S^p/\gamma_S) > 0.26$. This is confirmed from the results in Tables 1 and 3, for lactose ($\gamma_S^p/\gamma_S = 0.48$) and dicalcium phosphate ($\gamma_S^p/\gamma_S = 0.54$) with all the granulating liquids used, and for starch ($\gamma_S^p/\gamma_S = 0.41$) but only with the low viscosity granulating liquid. The last indicates that viscosity of PVP solution affects the film formation around the particles and their bonding into the granules. The coefficient λ_{LS2} is always negative, varying

Table 2
Contact angle of aqueous PVP granulating solutions with parafilm, density and components (dispersion and polar) of their surface tension

Aqueous PVP solution[a] (%w/v)	Contact angle with parafilm (θ°) (S.D.)[b]	Density (g ml^{-1})	Surface tension components (N m)		
			Dispersion γ_L^d	Polar γ_L^p	Total γ_L (S.D.)
K30-5%$_L$	107 (3.7)	1.100	15.7	39.3	55 (2.2)
K30-12%$_L$	111 (3.0)	1.110	12.4	37.6	50 (4.6)
K15-10%$_L$	105 (1.7)	1.100	17.0	38.0	55 (1.5)
K15-24%$_L$	105 (3.8)	1.096	13.7	37.3	51 (2.3)
K30-5%$_S$	102 (2.3)	1.007	21.6	37.4	59 (2.8)
K30-12%$_S$	104 (2.2)	1.010	13.1	45.9	59 (0.7)
K30-5%$_{DPD}$	109 (0.3)	1.007	14.3	44.7	59 (2.6)
K30-12%$_{DPD}$	123 (1.2)	1.010	9.7	43.3	53 (1.1)
Water	109[c]	1.000	23.2	48.8	72

[a] Saturated with diluent (L, lactose; S, starch; DPD, dicalcium phosphate dihydrate).
[b] S.D., Standard deviation
[c] Taken from literature (Malamataris and Pilpel, 1982).

Table 3
Contact angle, work of adhesion and spreading coefficients between PVP granulating liquids and diluents ($\lambda_{LS} = W_a - 2\gamma_L$ and $\lambda_{SL} = W_a - 2\gamma_S$)

Aqueous PVP solution (%w/w)	Contact angle θ(°) (S.D.)	Work of adhesion (mN m^{-1})		Spreading coefficient (mN m^{-1})			
		W_{a1}[a]	W_{a2}[b]	λ_{LS1}	λ_{LS2}	λ_{SL1}	λ_{SL2}
K30-5%$_L$	29 (3.2)	118	103	8.3	−6.9	−26.5	−41.7
K30-12%$_L$	38 (2.9)	109	89	9.8	−10.6	−35.0	−55.4
K15-10%$_L$	30 (1.4)	120	103	9.6	−7.4	−25.2	−42.2
K15-24%$_L$	37 (1.5)	112	92	10.5	−10.3	−32.5	−53.1
K30-5%$_S$	45 (1.5)	118	101	0.04	−17.3	−12.6	−29.9
K30-12%$_S$	56 (4.4)	107	92	−10.9	−26.0	−23.6	−38.6
K30-5%$_{DPD}$	33 (4.9)	121	109	3.0	−9.5	−17.8	−30.3
K30-12%$_{DPD}$	41 (1.0)	110	94	4.0	−13.0	−28.8	−45.8

[a] W_{a1}, Calculated from dispersion and polar components of the surface energy of diluents and granulating solutions.
[b] W_{a2}, Calculated from the contact angle θ of the granulating solutions on diluents.

Table 4
Mixing resistance (torque) and consumption of aqueous PVP solutions (ml and *S*%) corresponding to the boundaries of different agglomeration states (S_3, S_4 and S_5) for the diluents employed

Diluent/PVP solution (%w/v)	Torque (N m)			Liquid addition (ml) and *S*%					
	S_3	S_4	S_5	S_3		S_4		S_5	
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	S%	Mean (S.D.)	S%	Mean (S.D.)	S%
Lactose									
K15-10%	0.60 (0.07)	0.47 (0.12)	1.40 (0.07)	12.0 (0.8)	9.8	24.0 (1.6)	17.7	31.5 (1.5)	22.0
K15-24%	0.70 (0.07)	0.90 (0.08)	1.30 (0.08)	9.0 (0.8)	7.5	26.0 (1.4)	19.0	32.0 (2.1)	22.5
K30-5%	0.70 (0.08)	0.70 (0.06)	1.25 (0.03)	10.5 (0.7)	8.6	25.0 (1.0)	18.5	31.0 (2.1)	21.8
K30-12%	0.90 (0.03)	0.75 (0.08)	1.30 (0.06)	11.2 (0.5)	9.1	24.5 (1.0)	18.0	29.0 (1.3)	20.6
Starch									
K15-10%	0.65 (0.07)	1.00 (0.07)	2.40 (0.11)	67.5 (2.1)	43.5	109.0 (4.9)	55.4	141.0 (2.1)	61.6
K15-24%	0.65 (0.07)	1.00 (0.07)	2.00 (0.08)	62.5 (0.7)	41.6	112.0 (2.8)	56.1	129.0 (2.1)	59.5
K30-5%	0.60 (0.01)	1.00 (0.01)	2.75 (0.07)	69.5 (0.7)	44.0	95.0 (1.4)	51.9	125.0 (4.2)	58.7
K30-12%	0.90 (0.04)	1.00 (0.01)	2.70 (0.01)	72.0 (2.8)	44.1	109.0 (1.4)	55.4	128.0 (0.7)	59.3
DPD									
K15-10%	0.65 (0.07)	1.00 (0.01)	3.35 (0.21)	17.0 (0.2)	18.9	50.0 (0.2)	40.5	58.5 (2.1)	44.4
K15-24%	0.35 (0.07)	0.65 (0.07)	2.70 (0.28)	12.0 (0.1)	14.2	36.0 (1.4)	33.0	53.5 (0.7)	42.1
K30-5%	0.45 (0.07)	0.70 (0.14)	3.30 (0.29)	13.5 (0.7)	15.6	44.0 (1.4)	37.5	53.5 (2.1)	42.2
K30-12%	0.35 (0.07)	0.70 (0.14)	2.30 (0.28)	10.5 (0.7)	13.4	39.5 (0.2)	35.0	53.5 (2.1)	42.1

from -26.0 to -6.9 mN m^{-1} and hence it does not provide a clear indication of the spreading tendency. It is, however, highly correlated with λ_{LS1} ($r = 0.927$) and can be used comparatively to estimate the spreading tendency. Besides, it is easier to be determined than λ_{LS1}, since it requires only one contact angle determination (granulating liquid on diluent).

The values of the spreading coefficients of solid on liquid λ_{SL} (Table 3), are all negative and far from the corresponding values of λ_{LS}. It shows that in general, spreading of the diluents on the granulating liquids will not be favored and that all systems under investigation will behave similarly during the overwetting testing or that the examined wet agglomerates are formed in a similar way. In general, the λ_{SL} values are greater for the granulating liquids of lower viscosity. Also, as it was the case with the liquid on solid spreading coefficients, high correlation ($r = 0.975$) was found between λ_{SL1} and λ_{SL2} and hence λ_{SL2} can be used comparatively to estimate the spreading tendency of diluent on granulating liquid.

In Fig. 3 are shown typical profiles of torque exerted on the mixing vessel during the overwetting tests of the diluents and in Table 4 are summarized the values of torque and consumption of aqueous PVP granulating solutions (ml and S%) corresponding to the boundaries of the agglomeration states.

From the results of Table 4 appreciable differences are revealed between the values of both torque and liquid consumption. In order to test the significance and evaluate the importance of the effects of the applied experimental variables (independent variables) on the torque exerted on the mixing vessel and on the consumption of granulating solution (dependent variables), the results presented in Table 4 were subjected to statistical analysis. They were treated according to a split plot experimental design with one blocking factor (molecular weight), two whole plot factors (diluent, viscosity) and one subplot factor (agglomeration state). This design permits evaluation of all main effects as well as interactions between whole plot and subplot factors (Montgomery, 1987). Any interactions with the blocking factor are assumed as not important and go in the experimental error.

The results of the statistical analysis are given in Table 5 as F-statistic, significance (P) and η^2. The last parameter provides an indication of how well a certain factor explains the changes in the dependent variable and can be considered as a measure of the relative importance of its effect, with a maximum value of 1. From Table 5, it can be seen that as expected, the type of diluent and the agglomeration state exert the strongest effect on both torque and liquid addition ($P \leq 0.001$, $\eta^2 \geq 0.930$). The viscosity of granulating liquid has a significant effect on torque ($P = 0.033$, $\eta^2 = 0.632$) but not on liquid consumption, and the molecular weight of the binder does not affect either of these two variables.

Furthermore, from the results in Table 4 it is seen that torque at the pendular state (S_3), is becoming highest for lactose and starch and lowest for dicalcium phosphate dihydrate diluent,

Table 5
ANOVA for the results of overwetting tests

Factor	Torque (N m)			Liquid addition (S%)		
	F	P	η^2	F	P	η^2
PVP molecular weight	2.98	0.145	0.374	1.43	0.286	0.222
Diluent	33.03	0.001	0.930	1318.74	0.000	0.998
Viscosity	8.59	0.033	0.632	3.33	0.128	0.400
Diluent ÷ viscosity	12.38	0.012	0.832	3.52	0.111	0.585
Agglomeration state	145.88	0.000	0.960	823.11	0.000	0.993
Agglomeration state ÷ diluent	18.99	0.000	0.864	45.99	0.000	0.939
Agglomeration state ÷ viscosity	4.33	0.038	0.419	0.44	0.651	0.069

with the more viscous solution of higher molecular weight PVP (K30-12% w/v). In the funicular state (S_4) the torque is highest for starch, in general, and lowest for lactose with the less viscous solution of low molecular weight PVP (K15-10% w/v). In the capillary state (S_5), torque is lowest for lactose with PVP (K30-5%) and highest for dicalcium phosphate with PVP (K15-10%).

In general, lactose shows smoother increase of torque with agglomeration state (mean torque for: $S_3 = 0.73$, for $S_4 = 0.76$ and for $S_5 = 1.33$ N m) compared with starch (for $S_3 = 0.70$, for $S_4 = 1.01$ and for $S_5 = 2.46$ N m) and dicalcium phosphate (for $S_3 = 0.45$, for $S_4 = 0.76$ and for $S_5 = 3.16$ N m). This explains the significant interaction between type of diluent and agglomeration state, seen in Table 5. Furthermore, considering the changes of torque independently of agglomeration state and molecular weight, it is seen from Table 4 that for lactose the torque increases slightly with the viscosity or the PVP concentration (from 0.90 to 0.98 N m). On the contrary, for the case of dicalcium phosphate, the torque decreases appreciably with viscosity (from 1.59 to 1.18 N m) and for the case of starch torque decreases slightly with the increase of the viscosity (from 1.40 to 1.38 N m). The different behavior of diluents associated with the effect of viscosity on torque results in the significant interaction seen in Table 5.

The reduction in the torque with the viscosity may be thought as unexpected since higher viscosity means greater resistance to deformation for the mobile interparticle (liquid) bridges developed within the agglomerates and greater resistance in wet mixing or greater torque. Since during granulation adhesion of the wetted mass to the wall of mixing vessel did not occur, presumably the torque reduction with the increase of viscosity is caused from reduction in the attractive (tensile) and in the frictional (shear) forces operating between the wet agglomerates. This reduction should be due to reduced deformability of the liquid mobile bridges. They keep the wet agglomerates apart and reduce the attractive forces or are acting more efficiently as hydrodynamic lubricants reducing the frictional (shear) forces and finally the resistance during the wet massing or the torque exerted on the mixing vessel (Ritala et al., 1986; Parker et al., 1990).

A small increase of torque with molecular weight of binder is seen in Table 4 for starch, in the capillary state, at both viscosity levels. This may be related to adsorption of the PVP molecules on the diluent surface, which is probably greater for the larger PVP K30 molecules, resulting in increased liquid mobility, in increased deformability of wet bridges and higher torque response. A small, marginally significant interaction between viscosity, and agglomeration state, is also seen in Table 5.

Turning to the results on the consumption of granulating liquid (S%), it is seen from Table 4 that at any agglomeration state this is highest for starch and lowest for lactose. A small decrease of consumption with viscosity is noticed for dicalcium phosphate at both low and high molecular weight of binder. For starch and lactose the liquid consumption does not change remarkably neither with viscosity, nor with the molecular weight of PVP.

Considering the increase of liquid consumption from state S_3 to states S_4 and S_5, independently of viscosity and molecular weight, it can be seen that this is proportionally smaller for starch (mean consumption at $S_3 = 43.4$ $S_4 = 54.7$ and $S_5 = 59.8$%), when compared either with lactose (at $S_3 = 8.8$, $S_4 = 18.3$ and $S_5 = 21.7$%) or with dicalcium phosphate (at $S_3 = 15.5$, $S_4 = 36.5$ and $S_5 = 42.7$%). This explains the significant interaction between diluent and agglomeration state seen in Table 5.

Besides the aforementioned effects on the wet mixing parameters (torque and liquid consumption), the effects of the diluent and of the properties of PVP solution can be further elucidated by correlating with the solid–liquid interactions (work of adhesion and spreading coefficients). Attempts to plot liquid consumption (S%) at the mid-state of funicular agglomeration $(S_3 + S_4)/2$ versus work of adhesion confirmed earlier findings that they are inversely related (Malamataris and Kiortsis, 1997), but only for the high viscosity granulating liquids. The reason that no such result was found for the low viscosity granulating liquids can be explained due to the small changes in

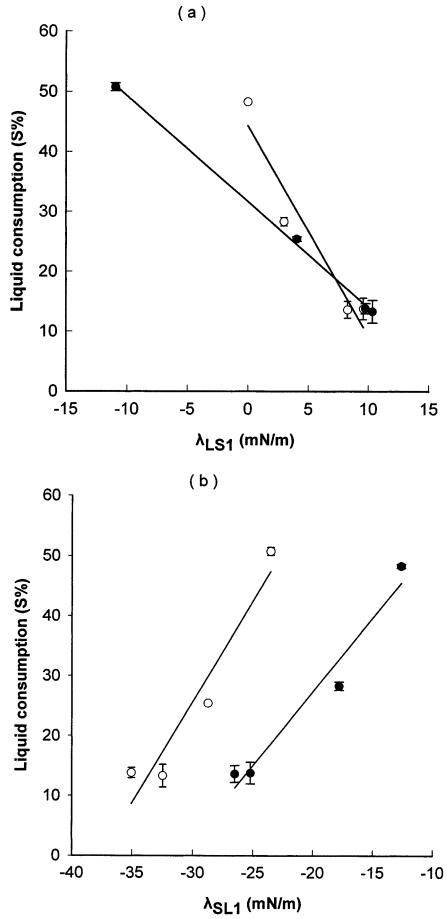

Fig. 4. Plots of granulating liquid consumption at the mid-state of funicular agglomeration versus spreading coefficient of liquid on solid (a) and solid on liquid (b) at low (●) and high (○) viscosity level. Bar represents ± S.D., $n = 3$.

W_a values (only water was used as solvent in the granulating liquid), and due to the predominance of other contributing factors. Furthermore, as expected, no correlation was found between torque and work of adhesion (Malamataris and Kiortsis, 1997).

Liquid consumption (S%) at $(S_3 + S_4)/2$ was also plotted (Fig. 4) versus the spreading coefficients. It can be seen that straight line relationships of good correlation (significant at $P = 0.05$) are obtained at both viscosity levels studied. The correlation coefficients for the low and for the high viscosity granulating liquid, respectively, are: for S% versus λ_{LS1} (Fig. 4a), $r = 0.999$ and 0.963; for S% versus λ_{LS2} (not shown), $r = 0.979$ and 0.983; for S% versus λ_{SL1} (Fig. 4b), $r = 0.979$ and 0.959, and for S% versus λ_{SL2} (not shown), $r = 0.850$ and 0.917. From Fig. 4 it is also seen that liquid consumption is inversely related to λ_{LS} but increases with λ_{SL}. This is expected since higher λ_{LS} represents easier spreading and better distribution of granulating liquid in the diluent, thus, reducing the amount of liquid required to reach the funicular state. On the other hand, higher λ_{SL} represents increased adherence of diluent powder to the binder solution, which hinders the formation of binder film around its particles, thus, increasing the amount of granulating liquid required for the funicular state.

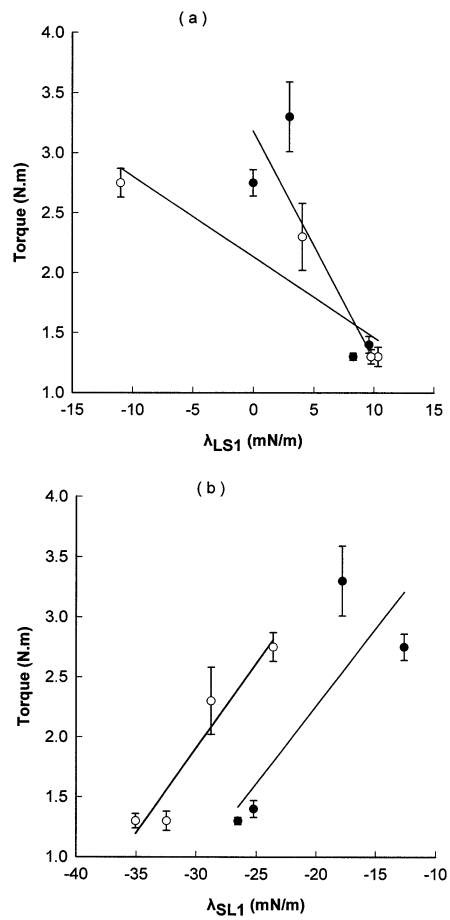

Fig. 5. Plots of torque exerted on the mixing vessel at the capillary state (S_5) versus spreading coefficient. Bar represents ± S.D., $n = 3$ (key as in Fig. 4).

No relation was found between the spreading coefficients and the torque measured at the pendular or funicular state. However, when the maximum torque reached at the capillary state (S_5), is plotted versus the spreading coefficients λ_{LS} and λ_{SL}, Fig. 5, it is seen that for the high viscosity binder solution, the points form straight lines with good correlation and significance level $P = 0.07$, $r = 0.924$ (Fig. 5a) and $P = 0.04$, $r = 0.959$ (Fig. 5b). For the low viscosity binder solution the relations are not significant, although the data appear to follow the same trend. As it was the case with liquid consumption, from Fig. 5 it is also seen that torque decreases with λ_{LS} but increases with λ_{SL}. This can be attributed to the easier spreading and distribution of granulating liquid with high λ_{LS} or low λ_{SL} value, as explained above for liquid consumption. The plots in Figs. 4 and 5 can be of practical significance, since from knowledge of the spreading coefficients, prediction can be made of the required amount of granulating liquid as well as of the maximum torque response reached during granulation.

3.2. Migration of drug in wet granulation during drying

Migration of propranolol hydrochloride during drying of wet granulations, quantified as coefficient of variation for its content in the five layers of the drying-cell (CV%), is given in Table 6. Furthermore, packing fraction (p_f) of the wet granules in the drying-cell, achieved by applying a standard procedure (p_f = bulk/apparent particle density = 1 − porosity), their liquid content (S%), apparent particle density and weight loss on drying (% w/w), are also given in Table 6 for the agglomeration states S_3, S_4 and the mid-state of funicular agglomeration $S_m = (S_3 + S_4)/2$. They were selected as parameters describing the distribution of the granulating liquid in the bed of wet granules placed in the drying cell. From Table 6 it can be seen that packing fraction is slightly different for the three diluents and also it appears increasing from pendular to funicular state. Higher density granules with lower packing fraction in the drying cell are obtained from dicalcium phosphate dihydrate, whereas granules with lowest density and highest packing fraction are produced from starch. The weight loss on drying, which is proportional to liquid consumption (S%), is as expected highest for starch and lowest for lactose.

From the results in Table 6 it can be seen that CV% is remarkably lower when drying is performed in the microwave oven. It is also seen that for all diluents, drying in the conventional oven, results in lower CV% for the pendular (S_3) than that for the funicular agglomeration state (S_4). This also applies, to microwave drying of starch and dicalcium phosphate dihydrate granulations, but only for the high viscosity binder solution. Although, microwaves act by penetrating and heating the bed of granules and vaporising water throughout the mass, in cases of high water content, the released vapor may condense on the nonporous sides of the drying-cell causing some drug migration (Copson, 1975).

In Table 7 are presented the results of analysis of variance, for the different agglomeration states (S_3, S_4 and mid-state S_m), concerning the effects of the type of diluent and of the viscosity of granulating liquid on drug migration and on their weight loss during conventional drying. It can be seen that the type of diluent has a strong effect on CV% at the funicular state ($P = 0.007$, $\eta^2 = 0.915$), but not at the mid state ($P = 0.179$, $\eta^2 = 0.821$) and the pendular state ($P = 0.192$, $\eta^2 = 0.562$). Among the three diluents, significantly higher CV% values at the funicular agglomeration state correspond to granulation containing lactose [Tukey's HSD (honestly significant difference) test] and lower to those containing starch. Between starch and dicalcium phosphate dihydrate there is not, however, significant difference, these two diluents forming a homogeneous subset. It was seen earlier, in Tables 2 and 3, that PVP granulating solutions saturated with these two diluents have similar values of surface tensions and that lactose (showing highest migration) has the lowest contact angle, whereas starch (showing lowest drug migration) has the highest contact angle with granulating liquid. Therefore, surface tension of granulating liquid as well as its contact angle with diluent are important factors in the migration of propranolol hydrochloride.

Table 6
Variability (CV%) in the content of propranolol hydrochloride for granulations at different agglomeration state containing different diluents and dried in conventional and microwave oven

Aqueous PVP solution (% w/w)	Agglomeration state			Apparent particle density (g cm^{-3})	CV% and loss on drying (% w/w) in oven:			
	(Si)	(p_f)	(S%)		Conventional		Microwave	
					(CV%)[a]	(% w/w)	(CV%)[a]	(%w/w)
Lactose								
K30-5%	S_3	0.30	8.6	1.47	8.8	3.1	3.0	5.1
K30-5%	S_m	0.29	13.6	1.49	21.2	10.3	–	–
K30-5%	S_4	0.33	18.5	1.45	31.9	13.0	4.1	11.9
K30-12%	S_3	0.30	9.1	1.44	6.9	6.1	3.4	5.3
K30-12%	S_m	0.31	13.6	1.48	10.4	9.6	–	–
K30-12%	S_4	0.35	18.0	1.44	21.4	11.7	2.8	10.2
K15-10%	S_3	0.28	9.8	1.48	8.5	6.8	4.7	6.6
K15-10%	S_4	0.32	17.7	1.44	36.6	12.5	4.0	8.2
K15-24%	S_3	0.29	7.5	1.49	4.5	5.2	1.7	4.7
K15-24%	S_4	0.33	19.0	1.45	22.6	11.7	4.4	8.6
Starch								
K30-5%	S_3	0.33	44.0	1.35	7.5	46.8	4.6	44.9
K30-5%	S_m	0.37	48.3	1.32	19.8	61.1	–	–
K30-5%	S_4	0.39	51.9	1.30	22.0	68.1	5.5	53.6
K30-12%	S_3	0.30	44.1	1.37	2.0	44.7	2.4	42.5
K30-12%	S_m	0.33	50.7	1.34	8.7	53.0	–	–
K30-12%	S_4	0.37	55.4	1.31	12.1	58.8	6.5	50.9
Dicalcium phosphate dihydrate								
K30-5%	S_3	0.23	15.6	2.25	4.4	8.2	5.4	10.5
K30-5%	S_m	0.24	28.3	2.09	18.9	17.4	–	–
K30-5%	S_4	0.30	37.5	1.94	28.3	22.8	5.4	20.2
K30-12%	S_3	0.24	13.4	2.27	2.7	9.7	2.5	8.0
K30-12%	S_m	0.25	25.4	2.13	4.7	19.4	–	–
K30-12%	S_4	0.23	35.0	2.02	14.0	20.2	7.2	30.4

[a] S.D. of CV% ≤ 0.6 ($n = 3$).
p_f, packing fraction; S%, liquid content %v/v.

Table 7
ANOVA for the effects of diluent and granulating liquid viscosity on drug migration (CV%) and loss on drying in the conventional oven

Measured property	State								
	S_3			S_m			S_4		
	F	P	η^2	F	P	η^2	F	P	η^2
Factor: diluent									
C.V.%	2.56	0.192	0.562	4.59	0.179	0.821	21.63	0.007	0.915
Weight loss	423.41	0.000	0.995	1261.21	0.011	0.989	307.46	0.000	0.994
Factor: viscosity									
C.V.%	5.51	0.079	0.579	120.60	0.008	0.947	71.37	0.001	0.984
Weight loss	0.03	0.873	0.007	0.56	0.531	0.220	4.20	0.110	0.517

Surface tension and contact angle of granulating liquid with diluent are taken into account in the expression of the liquid on solid spreading coefficient, λ_{LS}, which is related inversely to the liquid consumption (Fig. 4). From the plot in Fig. 6a it is also seen that liquid consumption at agglomeration state S_4 is inversely proportional to the CV% of drug content and, therefore, a relationship is expected between λ_{LS} and drug migration. This is shown in Fig. 6b for λ_{LS1} versus CV% and it is a direct linear relationship with correlation $r = 0.965$ ($P = 0.034$) for the low viscosity granulating liquid and $r = 0.90$ ($P = 0.10$) for the high viscosity liquid.

As it is also seen from Table 7, viscosity affects significantly drug migration at all agglomeration states, with increasing order from pendular ($P = 0.079$, $\eta^2 = 0.579$) to mid state ($P = 0.008$, $\eta^2 = 0.947$) and funicular ($P = 0.001$, $\eta^2 = 0.984$). Combining the effects of spreading coefficient and viscosity, CV% is plotted versus the ratio λ_{LS1}/viscosity, as shown in Fig. 7. It can be seen that the plot is a straight line with correlation $r = 0.903$ ($P = 0.002$), which accommodates all experimental data.

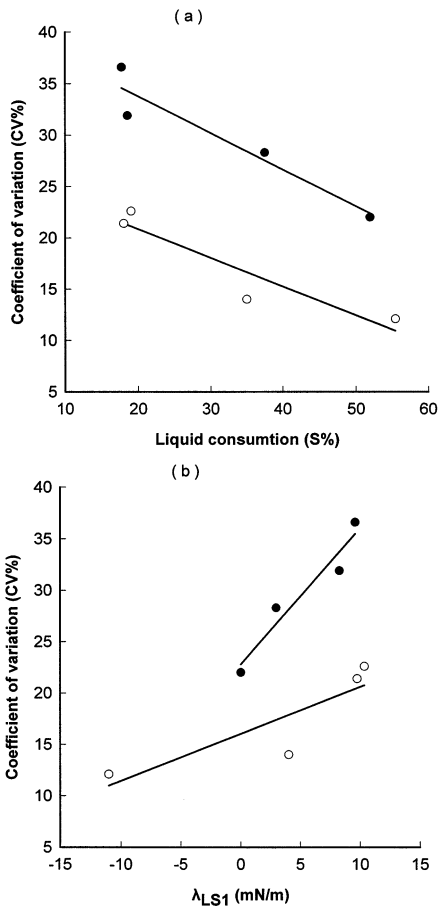

Fig. 6. Plots of CV% for drug content in the layers of drying-cell versus liquid consumption at funicular state (a), and spreading coefficient of liquid on solid (b) (key as in Fig. 4).

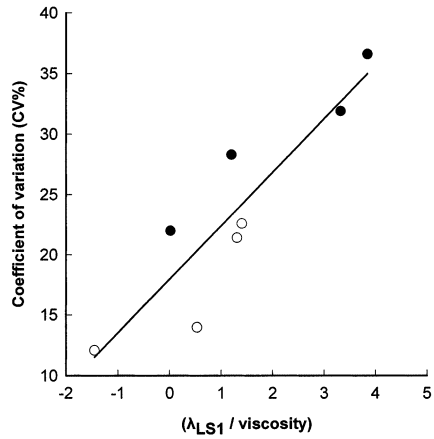

Fig. 7. Plot of CV% for drug content in the layers of drying cell versus the ratio λ_{LS}/viscosity, using all experimental data (key as in Fig. 4).

For granulations prepared with lactose (showing highest drug migration) and aqueous PVP solutions of certain viscosity but different molecular weight, there is not consistent change in the value of CV%. This can be seen from Table 6, since the CV% at the pendular agglomeration state (S_3) is higher for PVP-K30, while for the funicular agglomeration state (S_4) it is higher for PVP-K15. Therefore, for the granulation containing starch or dicalcium phosphate dihydrate, that show low CV% values, results with PVP solutions of different molecular weight, are not given in Table 6.

In addition to the liquid distribution (packing fraction and liquid content), solubility of the drug in the granulating liquid should alter its partitioning between the liquid and solid components (Warren and Price 1977a; Kiekens et al., 1999). Therefore, wet granulation and subsequent drying of drugs with different equilibrium solubility (prednisolone, salicylic acid, 1% w/w in diluent) were conducted, at conditions favoring maximum drug

Table 8
Variability (CV%) in the content of drugs of different solubility for granulations prepared at agglomeration state S_4 with lactose as diluent and dried in conventional oven

Drug	Solubility (ml required to dissolve 1 g) at				CV%
	25 °C		60 °C		
	H_2O	PVP K30 5%	H_2O	PVP K30 5%	
Prednisolone	14 000	3500–7000[a]	1555	400–770[a]	1.9
Salicylic acid	510	246	148	125	6.2
Propranolol HCl	7.0	12.5	2.0	1.8	31.9

[a] Manufacturer's literature data.

migration. Lactose was the diluent, low viscosity PVP K30-5% aqueous solution the granulating liquid, funicular the agglomeration state (S_4) and drying in the conventional oven. The results given in Table 8 show that CV% and migration increases with the solubility of the drug employed. Appreciable migration begins for salicylic acid with a solubility of 1 g in 148 ml of water and in 125 ml of PVP solution, at 60 °C, and becomes very high for propranolol hydrochloride with corresponding solubilities of 1 g in 2 and 1.8 ml. No migration of prednisolone is occurring during the drying and, therefore, it can be suggested, that migration may become a formulation problem for a drug when its solubility has a value >1 g in 148–400 ml of granulating liquid at the drying temperature applied.

4. Conclusions

In conclusion, migration of the water soluble drug propranolol hydrochloride, expressed as CV% of its content, was strongly dependent on the type of diluent. Also, the type of diluent exerted the strongest effect on torque and liquid consumption during wet kneading and a significant one on packing and moisture content of the final granulations. Viscosity of the granulating liquid affects significantly torque and drug migration, while the effect of molecular weight of the binder is not significant. Linear relationships of significance were found between spreading coefficients and the liquid consumption (S%) at the mid-state of funicular agglomeration $(S_3 + S_4)/2$ or the torque at the capillary state S_5. Migration of propranolol hydrochloride (CV%) was remarkably lower for drying in the microwave oven and increased from the pendular (S_3) to the funicular (S_4) agglomeration state when drying in conventional oven was applied. Linear relationships were found between migration of propranolol hydrochloride (CV%) and the spreading coefficient of liquid on solid (λ_{LS}), for the low and the high viscosity levels of the granulating liquid. Also, a general linear relationship accommodating all experimental data was found between migration (CV%) and the ratio of λ_{LS}/viscosity. Migration increases with drug solubility and may become a problem in a range higher than 1 g in 148–400 ml of granulating liquid.

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