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Granulations with surfactants: effects on pasting

M.N. Femi-Oyewo

Department of Pharmaceutics, University of Ife, Ile-Ife (Nigeria)

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Summary

When different types of surfactants were incorporated into binder solutions for the granulation of sulphanilamide (5% w/w), an anionic surfactant ('Manoxol OT') caused paste to be formed at the concentration where other surfactants tested produced normal granules. The effect of surfactants on the formation of pastes was considered essential for investigation. Four water-soluble surface-active agents at the usual level of concentration were incorporated into lactose-based powder blends in order to determine the effect of these agents on the massing in granulation. The presence of these surfactants caused pastes to be produced at lower liquid contents than those normally associated with pasting. The tendency of the effect observed was: anionic $\gg$ cationic $>$ non-ionic surfactants. Such pasting could not be linked with prolonged massing but with foaming and charges of the surfactant. Antifoaming agents when applied did not affect the properties of the granules and compacts.

Introduction

The first stage in the process of granulation is the wetting of the powder mixture (Carstensen et al., 1976), consequently the effectiveness of this step will affect the uniformity of moisture distribution and thus the properties of the final granules. This wetting can be affected significantly by the addition of a surfactant to a granule formulation (Aulton et al., 1977).

Binder distribution in powder granulation has been shown to be a function of mixing time (Carstensen et al., 1976). Excessive blending above that needed for the formation of equilibrium size granule, shifts the packing arrangement of the wet granule, causing it to become dense and non-porous (Zoglio et al., 1976). The damp mass formed during granulation can, if over-wet or on prolonged massing, form a paste which is totally unsuitable for further processing. A paste may be defined as a soft plastic mixture of the wet mass.

We have shown in a previous report (Femi-Oyewo and Spring, 1982) that the inclusion of 0.5% w/v surfactant in a binder solution led to the formation of a paste of 5% sulphanilamide during granulation with the anionic surfactants. However, cationic and non-ionic surfactants used at the same concentration did not cause pasting.

In the absence of surfactants, such wet paste is usually obtained as a result of either excess binder liquid or prolonged massing. In this study the possible factors responsible for the phenomenon of pasting obtained with surfactants in the granulation of pharmaceutical powders are considered.

Correspondence: M.N. Femi-Oyewo, Department of Pharmaceutics, University of Ife, Ile-Ife, Nigeria.

Experimental

Materials

The materials used were lactose (Whey), maize starch (BDH), polyvinyl pyrrolidone ('Plasdone' K_{29-32}, GAF, U.K.), 'Manoxol OT' (MOT) (BDH), which is dioctyl sodium sulphosuccinate, sodium lauryl sulphate (NaLS) (BDH), cetrimide ('CTAB') (ICI) and Cetomacrogol 1000 (C1000) (Texafor AIP, ABM Chemicals) were the surfactants tested.

Methods

Granulation. Granulation was carried out using blends of lactose [20 mm (mean particle diameter); 1.55 $g \cdot cm^3$ (true density)] 90% w/w and maize starch [14.2 mm (mean particle diameter); 1.51 $g \cdot cm^{-3}$ (true density)] 10% w/w. The binder was 15%, 17.5% or 20% by weight aqueous solution containing 7.5 g polyvinyl pyrrolidone (PVP) as well as the required weight of surfactant as needed. The binary powder mixture was pre-mixed in a Hobart Mixer for 4 min before the required weight of binder solution was added. Massing was to be carried out for 15 min but careful observations and timing were made for the onset of pasting. The effects of the following factors on pasting as a result of surfactant incorporation in the binder solution were determined:

(i) reduction in surface tension of binder solution;
(ii) change of surface charge on particles;
(iii) interaction between binder and substrate;
(iv) formation of a foam.

Effect of surface tension. Granulation was carried out as stated above but with 150 g of ethyl alcohol/water (distilled) blends of known surface tension values as the granulating fluid. The pasting time was observed, in order to show the effect of surface tension reduction in the absence of surfactant. The Drop-Volume method was used for the determination of the surface tension of the solutions.

Penetration ability studies. Lactose (BP or coarse) or sand was used as the bed in a column. Forty grams of lactose was gently tapped to a constant volume to effect proper packing of the material. Clean coarse sand (5 g) was then placed on top of the powder bed in order to prevent any disturbance of that bed's surface when the penetrating liquid was introduced. The surfactant solution (20 ml) of required concentration with or without PVP was introduced from the top at constant pressure head. The length of penetration of the liquid was measured with time. This was repeated using sand to eliminate the solubility effect of lactose.

The viscosity of the binder solutions was determined using a Rheomat 15 Viscometer.

Sedimentation/flocculation studies. The sedimentation volume of 100 g of lactose powder blend was determined by vigorously shaking the blend in each PVP (5% w/w)–surfactant (0.5 w/v) solution and this was left to stand.

For the flocculation studies, a saturated lactose solution in water provided a suitable suspension which was placed on a clean slide for microscopic examination/observation. This was repeated with a suspension prepared with 0.5% w/v of surfactant.

Foaming characteristics and effects. The development and effect of foaming by granulating fluids on pasting of powder blends during massing was studied. Such foaming characteristics as foam initiation (the ease with which foam is produced), foam volume or height and foam stability were studied.

Foam initiation was determined by vigorously shaking 200 ml of a binder solution containing 0.5% w/v surfactant, in a 250 ml measuring cylinder and the ease of foam formation and the level of the foam observed. The Ross-Miles (1941) method was used to determine the foam volumes (heights) as well as foam stability with only 0.5% w/v surfactant solutions.

An antifoaming agent – 'Antifoam A' concentrate (a silicone polymer) – was introduced into some of the systems in order to study the effect produced on the foaming characteristics shown with the granulating process.

Interaction–conductivity measurements. The conductivity of each of the ionic surfactants, MOT, NaLS and CTAB, in aqueous solutions was measured by means of a conductivity bridge (Cambridge Instrument Co.). Solutions were in the concentration range of 0.01–0.1% w/v. These were repeated using the same concentration range with 1.0%, 2.0% and 3.0% of lactose in order to observe any interaction between the surfactants and lactose.

Results and Discussion

The results of binder or liquid volume effect on pasting time are given in Table 1. In the presence of surfactants, the lactose-based powder blends formed pastes rapidly at much lower binder liquid volume than those normally associated with its pasting. This was due to improved wetting, while the blends produced pastes much more rapidly with anionic surfactants.

The relative ease with which the surfactants cause paste formation may be given as: MOT > NaLS ≫ CTAB > C1000. When pasting of powder beds does occur, the time taken for such pasting as shown in Table 1 becomes reduced with increasing surfactant concentration. Considering these data, it seems that there is a critical concentration of surfactants at which pasting will occur with various types of surfactants. The pasting time actually falls within the first 2 min of massing irrespective of the surfactant. Consequently prolonged massing will have no effect on pasting of powder blends in the presence of surfactants as pasting was critically within the short period of 2 min.

In the surface tension studies, there was no pasting at the end of massing with the ethyl alcohol/water mixtures (surface tension 33.24–23.04 $\text{mN}\cdot\text{m}^{-1}$ for 34%–96% alcohol, respectively) taken from Handbook of Chemistry and Physics (1967–1968). While some of the binder solutions with higher surface tension (Table 2) produced pastes, a surfactant solution (0.2% w/v NaLS, surface tension 29.5 $\text{mN}\cdot\text{m}^{-1}$) used alone without PVP in order to eliminate any PVP effect, on the pasting, resulted in a paste after 1.67 min of massing.

The fall in surface tension with increased surfactant concentration could not be regarded to be singularly enhancing pasting as is evidenced by the fact that ethanol/water mixes did not form pastes, whereas the same volume of the anionic surfactant solution, at similar surface tension gave a paste readily.

The rate of penetration as given by the Washburn equation below could be obtained from slopes of l^2 (cm^2) against t (min).

$$l^2/t = \frac{\text{Cos}\,\theta\cdot r}{2\eta}$$

where l is the length of penetration, in time t, of a liquid of surface tension γ, and viscosity η, with advancing contact angle θ, and r is the mean equivalent radius of the capillary passages through the powder. The values of the ratio of l^2/t of

TABLE 1

Pasting time of lactose/starch powder mixture (90:10) using 7.5 g PVP as binder – effect of binder volume, surfactant type and concentration

Surfactant conc.	Pasting time (min)											
	MOT			NaLS			CTAB			C1000		
	a	b	c	a	b	c	a	b	c	a	b	c
0	–	–	–	–	–	–	–	–	–	–	–	–
0.01	–	–	–	–	–	–	–	–	–	–	–	–
0.05	–	–	–	–	–	–	–	–	–	–	–	–
0.10	–	–	1.67	–	–	–	–	–	–	–	–	–
0.20	1.75	1.58	1.50	–	–	1.58	–	–	–	–	–	–
0.50	1.50	1.47	1.33	1.63	1.50	1.47	–	1.67	1.47	–	1.75	1.50

a = 15% by weight binder solution
b = 17.5% by weight binder solution
c = 20% by weight binder solution
– = no pasting after 15 min of massing

TABLE 2A

Surface tension (γ, $mN \cdot m^{-1}$) and viscosity (mPas) of binder solutions containing: 5% w/w PVP (7.5 g PVP) in 150 g binder solution

Surfactant concn (% w/v)	NaLS		CTAB		MOT		C1000	
	γ	η	γ	η	γ	η	γ	η
0.01	57.1	2.5	61.5	2.4	42.0	2.7	47.55	2.4
0.05	56.1	2.6	48.9	2.4		2.7		
0.10	52.2	2.6	38.8	2.5		2.7		
0.20	49.3	2.8	36.5	2.6	33.1	2.7	45.9	2.7
0.50	46.1	2.8	35.5	2.6	30.9	2.8	45.7	2.8

TABLE 2B

Surface tension (γ, $mN \cdot m^{-1}$) of penetrating aqueous surfactant solutions (0.5% w/v)

Surfactant	γ
MOT	29.9
NaLS	35.6
CTAB	32.4
C1000	41.0

water to that of the penetrating liquids through a powder bed are given in Table 3A.

The values of the ratio of penetration rate of water to that of surfactant are higher for the anionic surfactants especially MOT (Table 3A). This shows that the anionic surfactant solutions have lower penetration rates than either the cationic or the non-ionic surfactant solutions; in fact, the penetration rate was of the order: C1000 > CTAB > NaLS > MOT. Such an order gives an inverse relationship to the ratio values in Table 3A as well as the various time for paste formation.

The ratio of the penetration rates with water was generally reduced in the presence of PVP (Table 3A) and this could be due to viscosity effect of PVP solution since in Table 2, the viscosity of PVP solution alone is 2.7 mPas. The reduction in flow rates even though quite minimal for CTAB and C1000, the values for the two anionic

TABLE 3A

The ratios of penetration rate of water to that of surfactant solutions with and without PVP (5% w/w)

Material	Penetrating fluid	Ratio			
		MOT	NaLS	CTAB	C1000
Lactose BP	0.5% w/v surfactant solution	2.650	1.800	1.543	1.200
Lactose BP	0.5% w/v surfactant in 5% w/w PVP solution	1.700	1.542	1.458	1.132
Lactose (coarse)	0.5% w/v surfactant solution	1.452	1.323	1.081	1.048
Lactose (coarse)	0.5% w/v surfactant in 5% w/w PVP solution	1.118	1.059	1.041	1.029
Fine sand	0.5% w/v surfactant solution	2.273	1.364	1.236	1.018

TABLE 3B

The difference in ratios of penetration rates with and without PVP (5% w/w) as given in Table 3A

	Differences in ratio			
Surfactant:	MOT	NaLS	CTAB	C1000
Lactose BP	0.950	0.258	0.085	0.068
Lactose coarse	0.334	0.264	0.040	0.019

surfactants (MOT and NaLS), were significant as shown in the differences in Table 3B. The known interaction between PVP and anionic surfactants would explain such a phenomenon since cationic surfactants are not reported to show similar interactions (Saito et al., 1971; Arnarson et al., 1976).

Considering the order in surface tension values of the surfactant solutions used alone (Table 2B) and with PVP (Table 2A), that is, MOT < CTAB < NaLS < C1000 and MOT < CTAB < C1000 < NaLS, respectively, then surface tension results cannot fully account for the penetration results observed.

The sedimentation volumes of the powder mixture in 5% by weight PVP solutions with 0.5% w/v surfactants are given in Table 4. The speed of sedimentation and the ease of sediment dispersion were in the order of: C1000 > CTAB > NaLS > MOT; thus inversely related to the order of surfactant effectiveness in paste formation.

The observations from the flocculation studies were that no agglomeration or clumping together of the lactose particles occurred in the presence of surfactant solutions, and that there was thus no evidence from the results to suggest that the pasting of powders found to have been enhanced more in the presence of anionic surfactants than the cationic surfactant could be due to flocculation.

The foam initiation of both the anionic surfactants, MOT and NaLS, as well as the cationic surfactant, CTAB, were quite similar; but, however, different from those of the non-ionic surfactant, C1000. The PVP solutions containing the ionic surfactants caused foam to be produced at the top of the measuring cylinder ($\simeq 315$ cm^3) within a few seconds of shaking, while that of the non-ionic surfactant produced foam which did not reach the top of the cylinder even on prolonged shaking.

TABLE 4

Sediment volume of lactose/starch (maize)/powder mixture in PVP (5% w/w) solutions containing surfactants (0.5% w/w)

Time (h)	Sediment volume (cm^3)			
	MOT	NaLS	CTAB	C1000
0	30	50	70	100
0.5	30	50	70	102
1.0	31	50	70	104
18.0	35	54	72	104
21.0	88	94	98	100

The foam stability curves of the various aqueous surfactant solutions (0.5% w/v) are shown in Fig. 1, while the foam volume/height results as determined by the Ross-Miles method are given in Table 5.

It can be seen from these results that the ionic surfactants form foams readily while the non-ionic surfactant is a poor foamer. The stabilities of the foams from the anionics were similar, but differed from that of the cationic surfactant as they were less stable as shown by the higher liquid drainage volume. The volume of foam being produced has been shown to increase with surfactant concentration to a constant volume at the critical micelle concentration, CMC (Badwan et al., 1977); the CMC values for the surfactants, as indicated in Table 6, should give the tendency to paste in the order: MOT > NaLS ≫ CTAB > C1000; but since C1000 has the lowest CMC followed by MOT, it appeared that the CMC is less important than the charge on the surfactant when pasting is being considered. Furthermore it was noted that the surface tension values of the surfactant solutions cannot fully explain these results based on similar reasons.

The observation that the addition of Antifoam A concentrate, 50 ppm, to the binder solution containing 0.5% w/v MOT caused a wet mass with no pasting while the same solution alone produced highly aerated paste, becomes quite significant. It is possible to prevent pasting by the addition of an antifoaming agent.

It may therefore be inferred that the foaming obtained from the binder solution could have been facilitated by the method of preparation, i.e. stir-

TABLE 5

Foam volume, V (cm^3) and height (mm) of aqueous surfactant solutions (0.5% w/v) using Ross-Miles (1941) method

Time (min)	Foam volume, V (cm^3) (Height, mm)			
	MOT	NaLS	CTAB	C1000
0	275 (90.5)	265 (87)	276.5 (91.0)	195 (64)
5	75 (24.5)	205 (67)	244 (80)	150 (49)

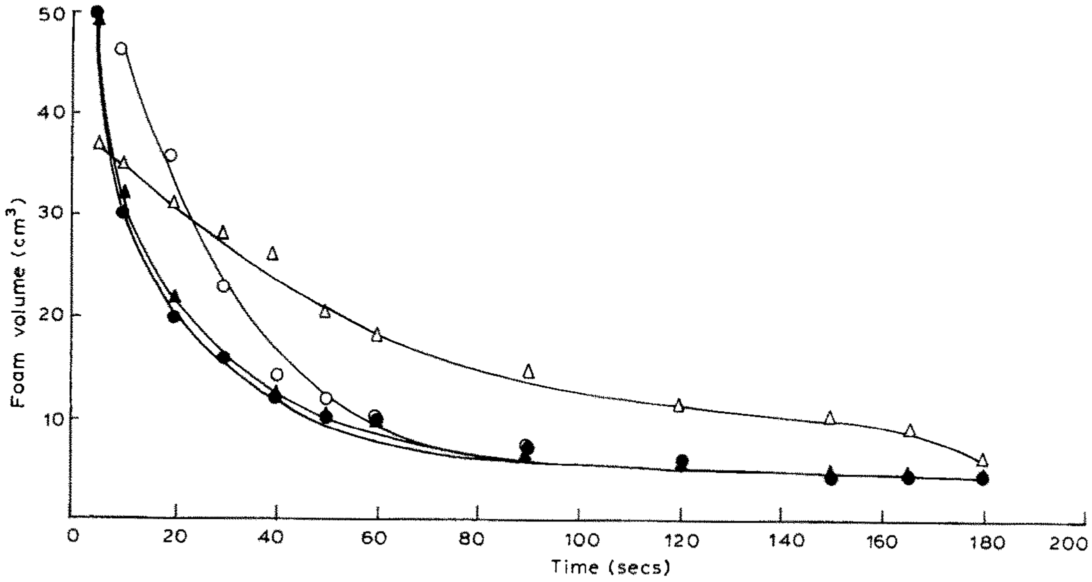

Fig. 1. Foam stability of 0.5% w/v aqueous surfactant solutions. ●, MOT; ▲, NaLS; ○, CTAB; △, C1000.

ring action of the mixer stirrer during massing in the presence of (anionic) surfactants. At high surfactant concentration, however, the binder solution no longer exists as a pure liquid, but contains a lot of foam which converts the granular mass into a plastic one. The foaming increases the apparent volume available for binding the powder particles. The charge on the surfactant could be significant in pasting since CTAB which had similar foaming ability as the anionic surfactants was not as effective as the anionics in paste formation. Addition of the antifoaming agent to the binder solution which contains MOT at the lower concentration of 0.1% w/v produced good granules but no significant effect on the mean size, the friability of the granules, nor the compact hardness as shown in Table 7. The methods used in this case: granulation, compaction, granule size and granule friability determinations, and compact hardness determination have been given in our previous study (Femi-Oyewo and Spring, 1982).

There was no indication from the results obtained from a correlative study of the equivalent and specific conductances of these aqueous surfactant solutions, with and without lactose, to show any interactions between these surfactants and lactose.

TABLE 6

The CMC values of the surfactants in water at 25°C (Mukerjee and Mysels, 1971)

Surfactant	CMC	
	mol·litre^{-1}	%
MOT	6.8×10^{-4}	0.030
NaLS	8.0×10^{-3}	0.23
CTAB	9.2×10^{-3}	0.34
C1000	3.89×10^{-10}	0.0004

TABLE 7

The properties of granules and the compact hardness of granules prepared from lactose (100%) using 15% w/w binder solution containing 0.1% w/v MOT, with and without an antifoaming agent

Antifoam A concentrate (50 ppm)	Mean granule size (μm)	% granule friability	Compact hardness (Kp)
Absent	290	5.30	3.40
Present	285	5.29	3.41

As the hydrophilic nature of the powder bed increased with increasing lactose content, so the concentration of surfactant required to form a paste decreased. The time taken for the lactose/starch blend (90 : 10) to form a paste was 1.75 min with 15% by weight binder solution containing 0.2% w/v MOT, while lactose/starch/sulphanilamide blend (85 : 10 : 5) did not form a paste after 5 min of massing under similar conditions. An increase in the concentration of the MOT in the binder to 0.5% w/v, however, produced a paste in 1.5 min.

Conclusions

These studies provide the following conclusions.

(1) In the presence of surfactants, lactose-based powder blends form pastes rapidly at much lower liquid contents than those normally associated with pasting.

(2) The greater the hydrophilicity of the powder blend, the lower the concentration of surfactant required before a paste is formed.

(3) Pasting in the presence of surfactants cannot be due to prolonged massing time as the time taken to form a paste is critically within the first 2 min of massing.

(4) The tendency to give pastes in such a system is in the order of: MOT > NaLS ≫ CTAB > C1000 (in effect, anionics ≫ cationic > non-ionic surfactant).

(5) Paste formation during massing of a powder blend in the presence of surfactants is linked with the formation of foam as well as the charge on the surfactant. Prevention of foaming by antifoaming agent does not affect the properties of the granules and compacts produced.

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