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A SCREENING STUDY OF LUBRICANTS IN WET POWDER MASSES SUITABLE FOR EXTRUSION-SPHERONIZATION

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ABSTRACT

Fourteen different substances were evaluated for their usefulness in reducing surface defects, heat due to friction and energy consumption in an instrumented extruder. The materials include several common lubricants and glidants, surface active agents, humectants, polyethylene glycol and a binder in a simple binary system with high drug loading. The substances under study were evaluated at two concentrations in a matrix composed of acetaminophen, Avicel PH-101 (70:30) and water. Maximum screen temperature, peak amperage draw, surface morphology of the extrudate, resistance to

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applied force, resistance to abrasion, surface morphology of the spheres, sphericity and size analysis were determined for each substance/concentration combination. High HLB surfactants, particularly SLS, performed best at levels as low as 0.125%, keeping heat and amperage draw to a minimum and greatly reducing surface defects.

INTRODUCTION

Formulas for extrusion-spheronization commonly have high drug loadings, up to 90%, which make them ideal for use in controlled release systems.[1] Active drug substances usually do not posses self lubricating properties, therefore there is a need for identifying substances which work at low concentrations reducing friction and surface defects. The various grades of Avicel have been studied extensively as matrix materials and other substances, such as binders and surface active agents, have been studied briefly.[2-6] The mechanics of flow have been characterized in a model system but no practical conclusions in terms of excipients have been offered to the formulator.[7-9] In this investigation, several substances were evaluated for their lubricating properties in a simple binary system with a relatively high drug loading. These substances include surface active agents, lubricants/glidants and humectants. The purpose of this study is to evaluate the effect these substances have, at low concentrations, on the extrusion-spheronization process and the properties of the spheres.

APAP was chosen as the model active ingredient because it is formulated at high percentages and because of its lack of cohesiveness[10] which probably makes it suitable for surface defect evaluations. A composition with 30% MCC and 60% water was chosen as the base because

it produced well formed spheres and generated a fair amount of heat and power drain.

EXPERIMENTAL

Materials

The core formulation includes: acetaminophen, USP (APAP, Mallinckrodt Inc., St. Louis, MO.) in a concentration of 70% and microcrystalline cellulose, NF (Avicel PH-101 [MCC], FMC Corporation, Philadelphia, PA.) in a concentration of 30%. The formula incorporated water at a concentration of 60% of total solids.

Classical tablet lubricants and glidants evaluated were: light mineral oil, USP (Squibb, New Brunswick, NJ.), magnesium stearate, NF (Mallinckrodt Inc., St. Louis, MO.), sodium stearyl fumarate (Edward Mendell Co. Inc., Paterson, NJ.), silicon dioxide, colloidal NF (Cabot Corp., Tuscola, IL.) and starch, NF (Staley Mfg. Co., Decatur, IL.).

Surface active agents included: sodium lauryl sulfate, NF (Stepan Co., Northfield, IL.), polysorbate 80, NF (ICI Americas Inc., Wilmington, DE.), glyceryl mono-oleate (Stepan Co., Northfield, IL.), sorbitan mono-oleate, NF and sorbitan mono-palmitate, NF (ICI Americas Inc., Wilmington, DE.).

Humectants and other substances consisted of: glycerin, propylene glycol, USP (Ashland Chemical Inc., Columbus, OH.) and hydroxypropyl cellulose, NF (Klucel type EF, Aqualon Co., Wilmington, DE.)

Manufacture of Spheres

All substances were incorporated at 1% and 3% levels in the control matrix. The trials were formulated to a

constant weight of 5 kg. by substituting an appropriate amount of Avicel. The process started by dry mixing in a planetary mixer (Machines Collette, model MP 20, Antwerp, Belgium) at 93 rpm for 5 minutes, the substances under evaluation were added at this stage. The mixer was then stopped and the speed reduced to 54 rpm. The mixer then re-started and water was added all at once through a top port, kneading continued for an additional minute after water addition. For all compositions, speeds at the extruder (Luwa Corporation, model EXDS-60, Charlotte, NC) and spheronizer (Luwa Corporation, model Q-400, Charlotte, NC) were set at maximum, 75 rpm and 1350 rpm respectively. The wet mass was extruded through a 1.2 mm. orifice screen and spheronized on a 2 mm. waffle plate. If the resulting mass was unsuitable for further processing after extrusion, then the experiment was stopped and only ease of extrusion was recorded (amperage and temperature). If there was reason to believe that the substance was effective at still lower concentrations, then these were tried. The spheres were collected on trays, dried in a forced air oven (Gruenberg Oven Company, model T08HX72.1SS1P, Williamsport, LA) at 45°C for 16 hours, or more, until a L.O.D. of 1 to 3% was achieved.

Evaluation of Spheres

The effect on process responses was evaluated by fitting the distal chamber of the extruder with a type K surface thermocouple (Omega Engineering, model 871, Standford, CT.) and the power supply with an ammeter (Mitchell Instruments, model TIF-1000, Miami, Fl.) capable of displaying peak and running amperage draw.

Ease of extrusion was assessed by measuring the amperage drawn by the extruder motor on a choke feed condition as well as recording the maximum temperature due to friction. Sphericity (shape factor: 1.0 is equal to a perfect sphere) was measured using an image analyzer (Cambridge Instruments, model Q-520, Cambridge, UK) which calculates this parameter by taking the ratio of the perimeter squared over area, times a constant ($S.F. = k \times P^2/A$). This test was performed on a 16-20 mesh cut. Surface defects were evaluated via visual examination using a microscope (Fisher Scientific, Stereomaster II model SPT-1TH, Pittsburgh, PA). Rank order was established by assigning samples to one of three categories. Resistance to abrasion was done by placing ten grams of a 16-20 mesh cut in an abrasion type friabilator (Van Kel, Edison, NJ.) with 200 glass beads (2-4 mm.) for ten minutes at 25 rpm. Size distribution was determined by sieve analysis (U.S. standard sieves) and resistance to diametral force was determined with a hardness tester (Vector-Schleuniger model THP-4M, Marion,IA).

RESULTS AND DISCUSSION

Ease of extrusion: In general, surfactants gave the best results in terms of lowering the amperage draw and maintaining the lowest temperatures at the extruder head. The baseline amperage found for this machine at maximum speed was 1.6 amperes (time allowed for stabilization was 30 minutes). In Table 1, additives are classified according to degree of effectiveness in reducing amperage draw and surface temperature on the extruder head. All surfactants at the 1% level, except glyceryl mono-oleate, were very effective. Surfactants reduced surface

TABLE 1
Temperature and amperage readings during extrusion

Substance	% added	Max. Temp.-°C	Peak Amps.	Δ Amps.
Control	-	41.3	3.9	2.1
<u>Very effective</u>				
Sorbitan mono-oleate	3	19.8	1.7	0.1
	1	22.8	2.0	0.4
Sorbitan mono-palmitate	3	20.5	1.9	0.3
	1	23.0	2.1	0.4
Sodium lauryl sulfate	1	23.7	1.8	0
	0.25	23.9	1.8	0
	0.125	24.8	1.7	0.1
Polysorbate 80	1	25.0	1.8	0
	0.25	27.0	1.8	0
Glyceryl Mono-oleate	3	27.7	1.8	0
Magnesium Stearate	3	21.5	1.8	0.2
<u>Moderately effective</u>				
"Klucel" (Aqualon)	1	29.5	2.1	0.5
Glyceryl mono-oleate	1	36.0	2.2	0.6
Sodium stearyl fumarate	3	23.4	2.3	0.5
Starch	3	24.3	2.4	0.8
Polyethylene glycol 3350	1	26.5	2.5	0.9
	3	24.0	2.2	0.6
<u>Ineffective</u>				
Glycerin	3	43.6	3.1	1.5
	1	40.0	3.9	2.3
Mineral oil	3	28.5	3.5	1.9
	1	43.6	4.9	3.3
Sodium stearyl fumarate	1	30.3	3.2	1.4
Propylene glycol	3	30.2	3.3	1.7
	1	32.7	3.6	2.0
Silicon dioxide	3	27.3	2.7	1.1
	1	30.1	2.8	1.2

TABLE 2
T test for temperature, additives at 1% concentration

	Surfactants	Non-surfactants
Mean max. temp.-°C	26.1	33.7
Variance	31.4	44.2
Sample size	5	6

t= 5.06, df= 9, significant difference ($p < 0.001$)

TABLE 3
T test for amperage, additives at 1% concentration

	Surfactants	Non-surfactants
Mean Δ current (A)	0.3	1.3
Variance	0.07	1.07
Sample size	5	6

t= 2.63, df= 9, significant difference ($p < 0.05$)

friction resulting in lower temperatures and current draw. Of these, sodium lauryl sulfate and polysorbate 80 produced no added power consumption at 1% and were still effective at lower concentrations. Lubricants and glidants, humectants and other substances were either moderately effective or ineffective. The only exception to this observation is magnesium stearate at 3%. Some trials did not progress past the extrusion step due to excessive agglomeration or excessive fines, these were sorbitan mono-oleate (3%), sorbitan mono-palmitate (3%), sodium lauryl sulfate (1%) and polyethylene glycol (3%). The difference in temperature and amperage for the surfactants, as a group, from other groups was statistically different (Tables 2 and 3).

Sphericity: Shape factor determinations via image analysis show that, generally, the resulting material deviated very little from a spherical shape. As can be seen in Table 4, only a few material/concentration

TABLE 4
Image analysis - shape factor, arranged by rank order

Substance	-n-	Mean	Std. dev.	
Control	44	1.223	0.053	
Sodium lauryl sulfate 0.125%	35	1.211	0.051	
0.25%	49	1.215	0.045	
Sodium stearyl fumarate 1%	51	1.221	0.050	
3%	38	1.224	0.056	
Glycerin 1%	58	1.256	0.066	
Glyceryl mono-oleate 1%	41	1.265	0.077	
Glycerin 3%	60	1.278	0.091	
Silicon dioxide 3%	34	1.286	0.062	
Klucel 1%	30	1.302	0.042	
Polysorbate 80 1%	38	1.304	0.152	
Propylene glycol 1%	44	1.313	0.188	
Polysorbate 80 0.25%	57	1.314	0.076	*
Propylene glycol 3%	34	1.340	0.209	
Mineral oil 3%	36	1.345	0.113	*
Silicon dioxide 1%	39	1.346	0.162	
Polyethylene glycol 3350 1%	32	1.349	0.315	
Glyceryl mono-oleate 3%	41	1.358	0.231	
Magnesium stearate 3%	39	1.364	0.134	**
Sorbitan mono-oleate 1%	35	1.383	0.110	***
Sorbitan mono-palmitate 1%	46	1.391	0.225	*
Mineral oil 1%	31	1.397	0.108	***
Starch 3%	33	1.413	0.141	***

* - denotes a significant difference from the control ($p < 0.1$)
** - denotes a significant difference from the control ($p < 0.05$)
***- denotes a significant difference from the control ($p < 0.02$)

combinations have statistically significant differences from the control.

For the substances found to be effective in reducing friction, it is a very desirable property to have since they affect minimally the shape factor. Of the substances that differed from the control, it was noted that differences were due to excessive agglomeration during spheronization. In the case of mineral oil were it was noted that deviations were caused by the adherence of fines.

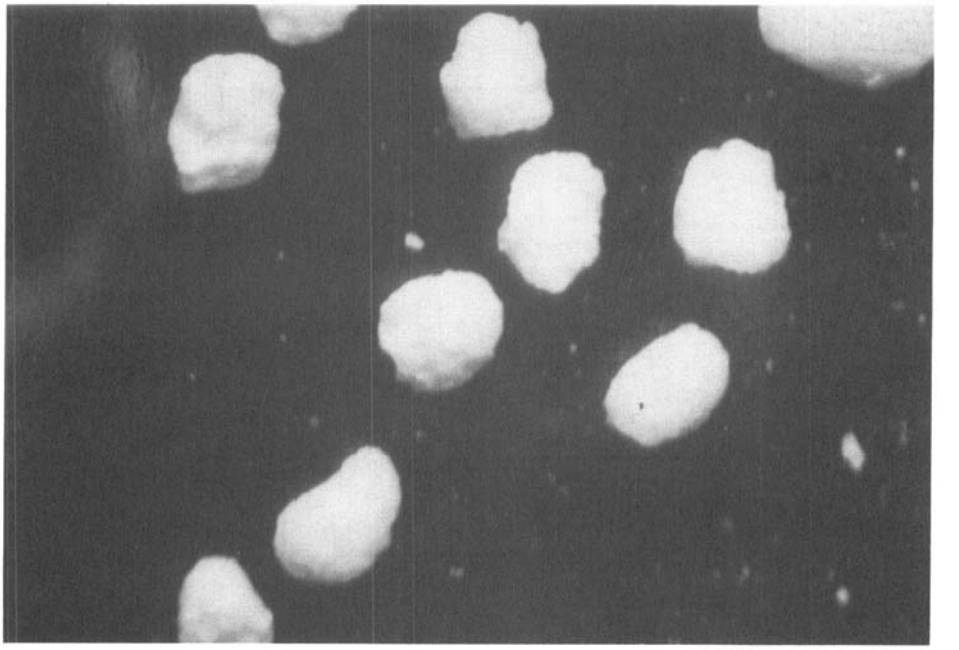

FIGURE 1
Spheres - control formulation

Surface defects: Figures 1 through 8 are photomicrographs of selected trials. Very smooth extrudate and spheres were formed when sodium lauryl sulfate was incorporated at 0.25 and 0.125% levels, as well as polysorbate 80 at 1%. This extrudate breaks evenly on spheronization and produces spheres with smooth surfaces. In contrast, additives such as magnesium stearate, silicon dioxide, and corn starch produce spheres with numerous surface defects and sharkskinning. Extrudate from other substances also had a high incidence of surface defects although not of the severity of those mentioned above. One notable exception was sodium stearyl fumarate which, at both concentrations tested, formed extrudate with surface defects but amazingly smooth spheres.

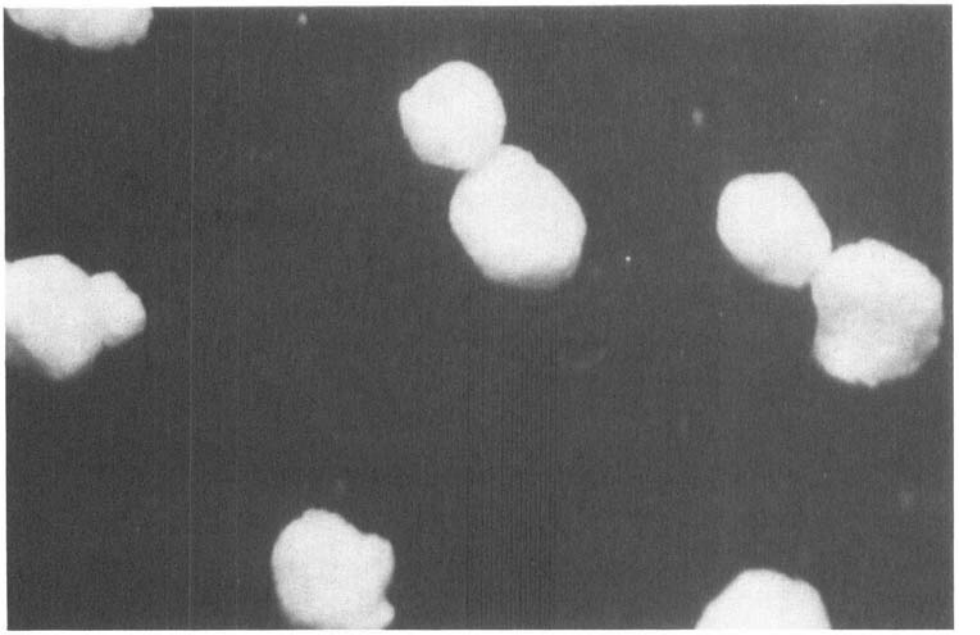

FIGURE 2
Spheres - sodium lauryl sulfate 0.25%

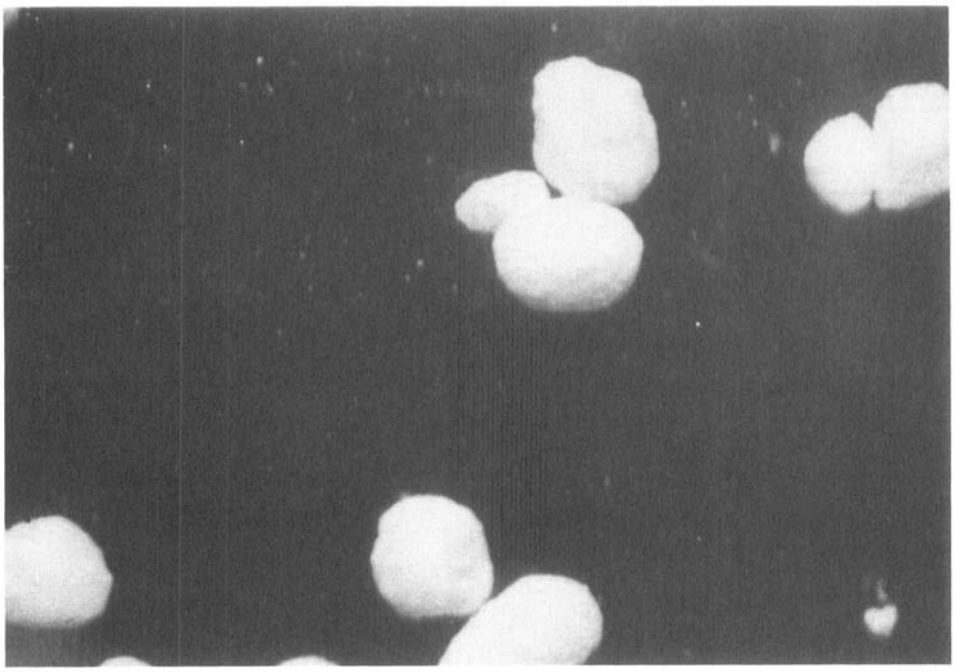

FIGURE 3
Spheres - sodium lauryl sulfate 0.125%

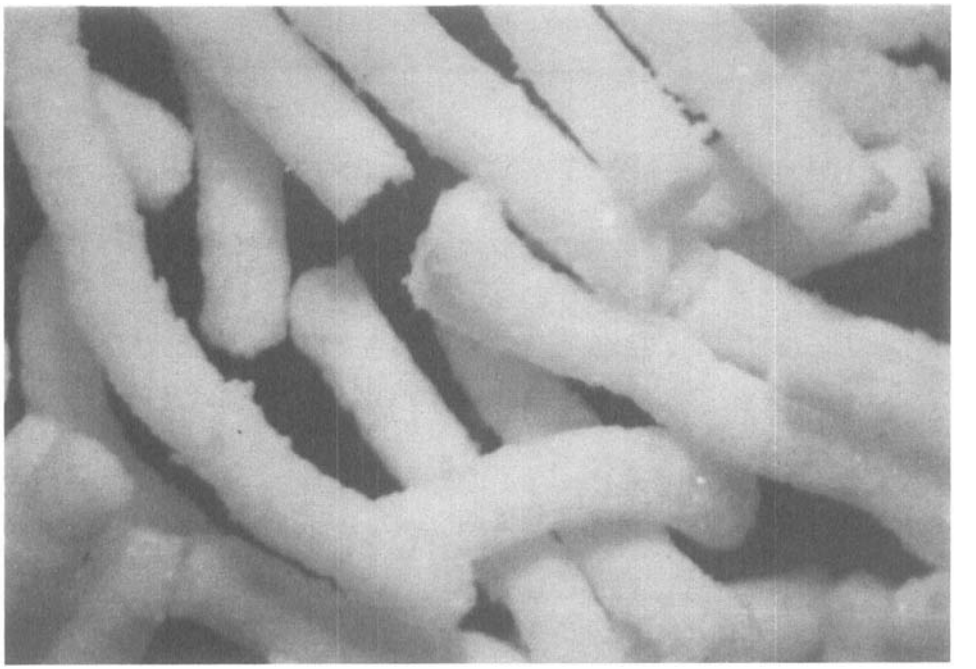

FIGURE 4
Extrudate - sodium lauryl sulfate 0.125%

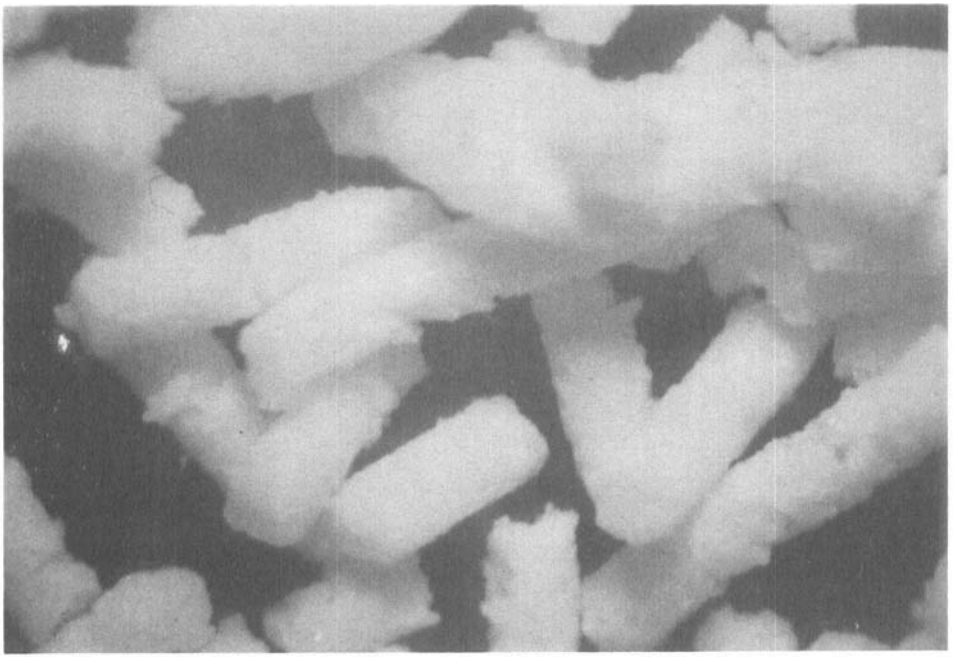

FIGURE 5
Extrudate - polysorbate 80 0.25%

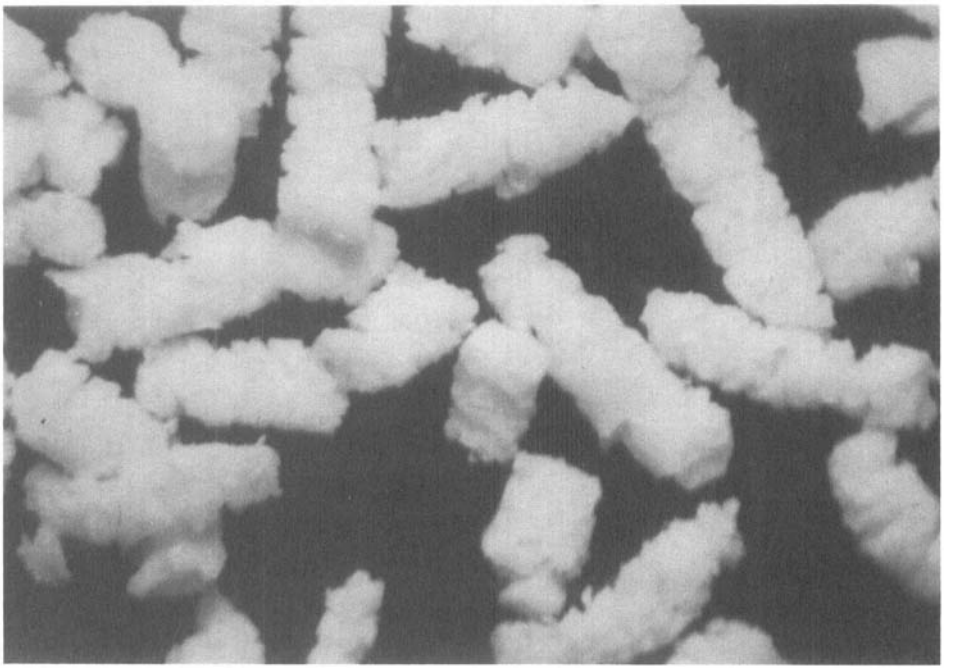

FIGURE 6
Extrudate - magnesium stearate 3%

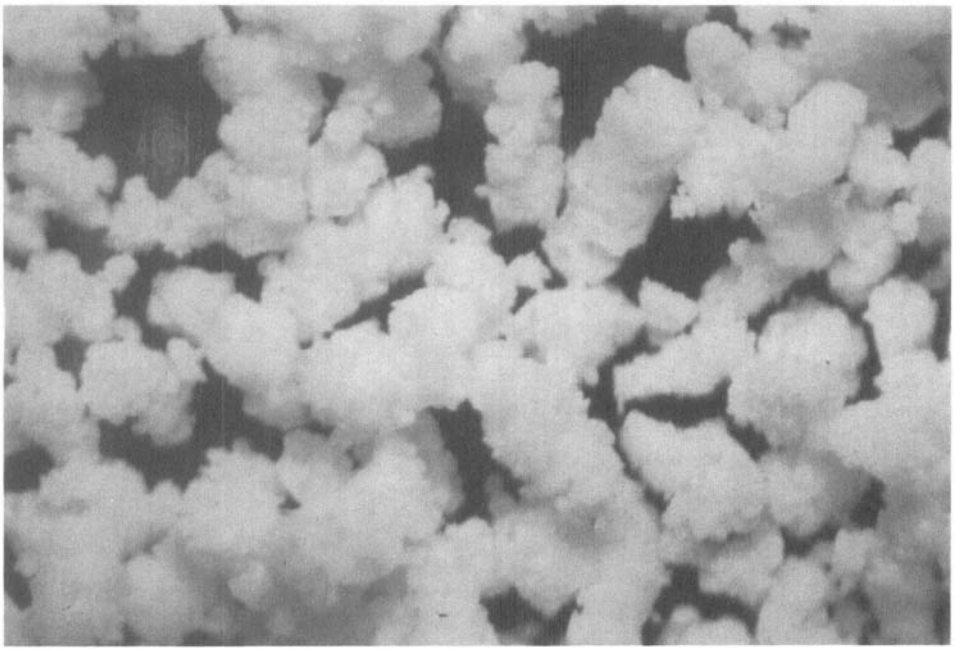

FIGURE 7
Extrudate - corn starch 3%

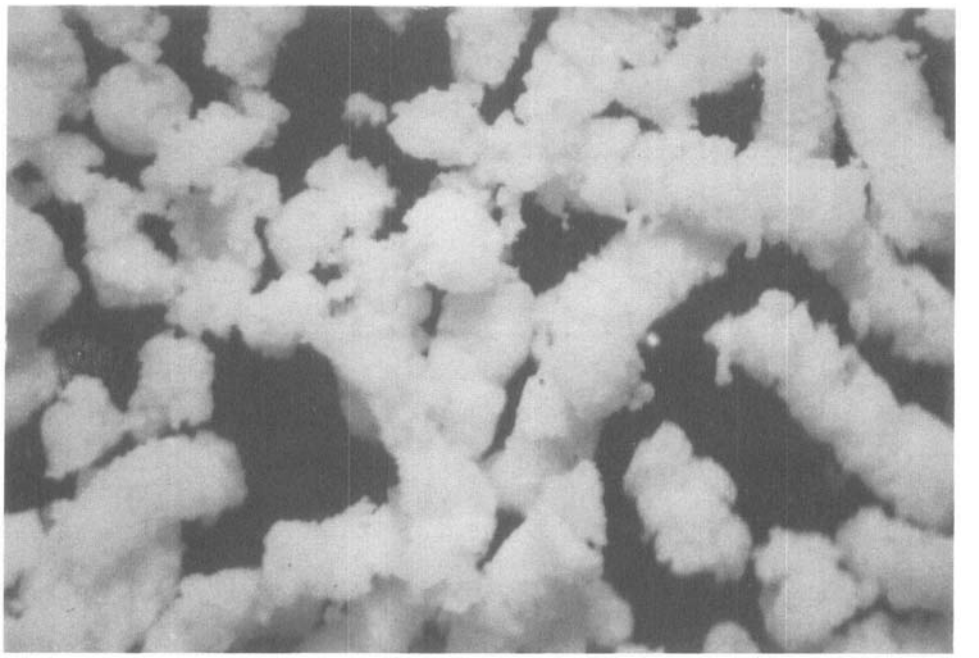

FIGURE 8
Extrudate - silicon dioxide 3%

Physical properties: The physical properties including size distribution, resistance to abrasion and resistance to diametral force are listed in Tables 5 - 7. From the group of combinations that could be spheronized, all additives tend to increase the size of the spheres as compared to the control lot. Some materials could not be spheronized due to excessive agglomeration; these were sorbitan mono-palmitate, sorbitan mono-oleate, PEG 3350, Klucel (3%) and sodium lauryl sulfate (1%). Starch and magnesium stearate at 1% created an excessive amount of fines and could not be spheronized. These substances at 3% levels also produced fines but spheres did form. These fines adhered to the coarser particles like satellites and produced misleading size distributions.

TABLE 5
Physical properties of spheres - surfactant additives

Substance	Control	SLS		P-80		GMO		SMP	SMO
Conc.- %	-	0.25	0.125	1	0.25	3	1	1	1
Resistance to abrasion									
% weight loss:	1.3	2.2	1.2	6.8	3.8	5.7	1.2	1.4	0
Mean resistance to applied force									
Newtons (n=30)	6.5	4.0	6.0	8.8	10.7	4.0	9.5	10.6	9.8
Size distribution									
% retained on									
14	1.7	71.3	67.7	78.5	67.0	72.1	42.9	78.9	83.8
16	4.6	13.7	15.8	8.5	11.7	8.9	14.9	9.4	6.5
18	15.9	8.2	8.3	5.5	7.7	5.9	11.7	3.3	2.4
20	8.9	4.9	4.7	4.0	7.7	6.1	13.1	3.8	3.0
30	8.7	2.6	2.1	2.6	4.9	4.8	10.9	3.5	1.5
PAN	60.2	0.9	0.5	1.0	1.0	2.2	6.5	1.4	0.5

TABLE 6
Physical properties of spheres - lubricants/glidants

Substance	Control	MO		Star	SSF		MgSt	SiO	SiO
Conc.- %	-	3	1	3	3	1	3	3	1
Resistance to abrasion									
% weight loss:	1.3	2.6	6.9	1.5	1.1	3.5	1.9	1.6	1.6
Mean resistance to applied force									
Newtons (n=30)	6.5	11.4	14.0	17.8	8.1	7.0	10.0	19.0	18.3
Size distribution									
% retained on									
14	1.7	19.7	10.5	67.8	89.0	17.2	97.4	72.3	29.5
16	4.6	21.4	10.0	18.0	7.0	20.9	1.6	15.9	22.2
18	15.9	20.1	12.3	4.5	3.0	20.4	0.4	6.9	16.6
20	8.9	19.6	14.7	4.9	0.8	15.6	0	3.7	18.0
30	8.7	15.5	19.4	0.9	0.2	12.4	0.4	0.8	12.0
PAN	60.2	5.5	34.3	0.3	0	13.5	0.4	0.3	2.1

TABLE 7
Physical properties of spheres - humectants and other additives

Substance	Control	P.gly.		Gly.		PEG	HPC
Conc.- %	-	3	1	3	1	1	1
Resistance to abrasion							
% weight loss:	1.3	1.5	0	0.3	2.3	1.8	0
Mean resistance to applied force							
Newtons (n=30)	6.5	14.2	13.3	10.6	13.8	18.7	9.2
Size distribution							
% retained on							
14	1.7	71.5	25.5	35.6	17.6	95.9	39.1
16	4.6	16.7	22.4	17.2	17.7	2.8	25.5
18	15.9	7.1	18.6	13.1	16.2	0.6	24.6
20	8.9	3.5	19.7	15.6	21.9	0.4	10.2
30	8.7	1.3	12.1	12.3	20.1	0.6	2.4
PAN	60.2	0.4	1.9	6.2	6.5	0.3	0.9

In terms of resistance to abrasion, only four additives appear to have values significantly greater than the control formulation. These were sodium stearyl fumarate, polysorbate 80, glyceryl mono-oleate and mineral oil.

In general, surface active agents produced spheres that were comparable to the control formulation when subjected to a breaking force. A concentration dependent effect is seen in that higher concentrations of a particular surfactant decreases resistance to an applied force. Other classes of additives yield either comparable or increased resistance to an applied force.

CONCLUSIONS

As a group, surfactants are considered to have performed best as additives to enhance extrudability by greatly reducing heat generation and facilitating the

exit of the formed wet mass from the extruder head. Within this class sodium lauryl sulfate was most effective working at concentrations as low as 0.125%. When compared to a control formulation this additive does not impact unfavorably physical characteristics such as resistance to abrasion or resistance to an applied force. The effect on size distribution can be easily offset by choosing an extruder screen that yields the desired size range. Sodium lauryl sulfate also produced a smooth extrudate with a low incidence of surface defects/ sharkskinning and suitable spheres. The absence of surface defects promotes uniform breakage of the extrudate during spheronization and minimizes fine particles resulting from the segmentation of deep ridges. This property is also useful if the formulated system is intended for controlled release since it affords the greatest control of surface area in the spheres. Other classes of additives were not considered as useful due to limited success in reducing friction and temperature at the concentrations of interest or because of untoward effects in the properties studied.

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