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RESEARCH PAPER

Preliminary Report of the Discovery of a New Pharmaceutical Granulation Process Using Foamed Aqueous Binders

Colin M. Keary* and Paul J. Sheskey*

Larkin Laboratory, The Dow Chemical Company, Midland, Michigan, USA

ABSTRACT

Spray granulation is commonly used to improve the flow of drug formulation powders by adding liquid binders. We have discovered a new granulation process whereby liquid binders are added as aqueous foam. Initial experiments indicate that foam granulations require less binder than spray granulations, less water is added to the powder mass, rates of addition of foam can be greater than rates of addition of sprayed liquids, and foam can be added in a single batch to the surface of the powder mass for incorporation at some later stage in the process. This new process appears to have no detrimental effects on granulate, tablet, or in vitro drug dissolution properties. In addition, the elimination of spray addition reduces the complexity of the process and avoids the plugging problems associated with spray nozzles. Several formulations were successfully scaled up from laboratory scale (1.5 kg) to pilot scale (15 kg). Process control was good and there was no detrimental effect on tablet and drug dissolution properties. This paper also proposes a working hypothesis of the mechanism by which foam granulation operates.

Key Words: Aqueous foam; High-shear granulation; Wet granulation; Foam granulation; Foamed binder; Cellulose ethers.

INTRODUCTION

Granulation literature is extensive and describes applications within many industries.[1–3] The pharmaceutical industry appears to publish more granulation reviews[4,5] and papers[6–8] than any other industry. According to Tardos[9] ''Granulation is the unit operation by which small powdery particles are agglomerated into larger entities called granules. Powder granulation and coating are done to improve flowability, appearance and mixing properties, to avoid dustiness and reduce segregation and, in general, to

*Correspondence: Colin M. Keary and Paul J. Sheskey, Larkin Laboratory, The Dow Chemical Company, Midland, MI 48674, USA; E-mail: cmkeary@dow.com; psheskey@dow.com.

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either eliminate undesirable properties or to improve the physical or chemical properties of fine powders.'' Tardos elaborates further[9] ''the most common way of granulating powders is by either using liquid binders in the form of a solution or melt, or by employing pressure to insure coalescence and growth.'' The theoretical treatment of granulation processes developed from the early work of Newitt and Conway-Jones[10] to the current efforts by the group led by Litster.[5,11]

Both immediate-release (IR) and controlled-release (CR) solid-dosage formulations are often prepared using a wet granulation process (i.e., liquid binder) to facilitate powder flow in gravity-fed tablet manufacturing. Typically, IR formulations are granulated by adding to the powder mass an aqueous solution of a binding polymer. CR formulations usually contain a polymeric excipient (e.g., 20–40 wt % hypromellose) in the powder mass,[12,13] and this polymer may also function as the granulation binder as a result of adding water during the granulation process. CR formulations may also be granulated by adding a solution of a binder polymer.

Although pharmaceutical companies successfully use wet granulation to prepare drug formulations, it is an equipment-intensive and worker-intensive manufacturing step. Hlinak has stated[14] that ''Batch granulation is well known for its complexity, instability and inherent variability.'' The lack of predictable behavior of the granulation process has complicated the development of suitable models, consequently the granulation process is often considered to require a trial-and-error approach.

Instrumental innovations to address the technical challenges of complexity, variability, and instability[14] have done little to remedy a major source of variability; namely, the use of spray nozzles for binder addition. Nozzles tend to clog, which can result in the loss of, or re-work of, an entire batch of a formulation. At a laboratory scale, wet granulations can be performed without the use of nozzles simply by adding the binder liquid slowly while the powder mass is in motion. However, this approach would be very difficult to control on a production scale.

Just selecting a spray nozzle for use in wet granulation is complex—one must consider nozzle type, nozzle geometry, spray geometry, location of nozzle, spray rate, and droplet size. Litster's group has performed a most comprehensive study of spraying[15] by defining and quantifying a ''dimensionless spray flux.'' Lengthy discussions[11] of uniform binder distribution and its influence on granule growth emphasize the importance of binder distribution. Theory matches performance for low-viscosity binder addition, e.g., when lactose is granulated with sprayed water. For more viscous binder liquids, such as hydroxypropylcellulose (HPC, 7%, 104 cP) and polyethylene glycol (PEG200, 64 cP), the process is dominated by mechanical dispersion.[11] Increased mechanical dispersion implies increased blade speeds and longer mixing times to efficiently mix the components.

This paper is a preliminary report of the discovery of a new granulation process using foamed aqueous binders that addresses many of the problems inherent to wet granulation. The effects of foam granulation on binder distribution, control of binder addition, processing time, tablet properties, and drug dissolution are shown in the results of a series of laboratory-scale and pilot-scale experiments. The paper also discusses the principles of binder foams and presents a working hypothesis for the mechanism of foam granulation of powders.

EXPERIMENTAL

Materials

The following materials were used:

Acetaminophen powder, USP, Spectrum Quality Products, Inc., New Brunswick, NJ

Croscarmellose sodium, NF, Ac-Di-Sol™, FMC Corporation, Philadelphia, PA

Dicalcium phosphate dihydrate, USP, Astaris LLC., St. Louis, MO

Diphenhydramine HCl, USP, Spectrum Quality Products, Inc., Gardena, CA

Hypromellose 2910, USP, METHOCEL[a] E3PLV, E5PLV, and E6PLV grades, and Hypromellose 2208, USP, K3PLV and K4MP grades, The Dow Chemical Company, Midland, MI

Lactose monohydrate, NF, modified spray-dried, Fast-Flo™ 316, Foremost Farms USA, Rothschild, WI

Magnesium stearate, NF, impalpable powder, Mallinckrodt Baker Inc., Paris, KY

Microcrystalline cellulose, NF, Avicel™ PH-102, FMC BioPolymer, Newark, DE

Naproxen sodium, USP, Pharmaceutical Fine Chemicals, S.A., Freeport, Bahamas

Polyethylene oxide, NF, POLYOX[a] WSR Coag, The Dow Chemical Company, Midland, MI

Polyvinylpyrrolidone, USP, Plasdone™ K-29/32, ISP Technologies, Inc., Wayne, NJ

[a]Trademark of The Dow Chemical Company.

Pre-gelatinized corn starch, NF, Starch 1500™, Colorcon, Inc., Westpoint, PA
Sodium lauryl sulfate, NF, Aldrich Chemical Company, Inc., Milwaukee, WI
Theophylline powder, USP, Knoll Pharmaceutical Fine Chemicals, Whippany, NJ

Note: Monograph USP26 has adopted the term ''hypromellose'' in place of ''hydroxypropyl methylcellulose.''

Foam Generation

The foam-generating equipment is based on an early design,[16] modified by incorporation of an air intensifier to enable foaming of viscous fluids. The air intensifier is a convenient way to generate air pressure of $\leq$150 psi from in-house air supplies that typically provide only 40–80 psi. Foam is typically added to the granulator bowl via a plastic pipe that is simply inserted through any convenient port that provides access to the granulator bowl. No nozzles are required; the foam is simply pumped into the bowl at any location where the blades will not be fouled by the pipe.

Laboratory-scale Granulation

Formulations

Table 1 lists the powder formulations used in the laboratory-scale granulations.

Granulation Methods

Laboratory-scale granulation experiments used a 10-L Powrex® (Glatt Air Techniques Inc., Ramsey, NJ) high-shear granulator equipped with a torque sensor. Three distinct modes of addition of the foamed binder were used: step-batch, continuous, and batch (described below). Rates of addition of foamed binder were 75 or 300 g/min, depending on the experiment. Foamed binder was delivered through the same 0.5-inch port located on the granulator lid used for conventional spray delivery and dispersed in the powder by running the granulator at room temperature, with side chopper blades at 1,800 rpm and the main blade at 300 rpm.

In the step-batch mode of foamed binder addition, an aliquot of foam was added to the powder for 60 s at 75 g/min liquid flow rate while the high shear granulator was running. The foam was homogeneously dispersed into the powder in the running granulator. The granulator was then stopped, and the granulate was examined visually and manually to qualitatively determine the degree of wetness and granularity. The procedure was repeated eight times, i.e., eight aliquots of foam were added for 60 s, each at 75 g/min flow rate, until an acceptable wetness and granularity were achieved. ''Acceptable'' was deemed to be the point at which a compressed handful of granulate would hold loosely together and easily break apart again into agglomerated particles. The step-batch mode may be considered as a ''learning mode'' to be used when formulators first encounter an unfamiliar powder system that has to be granulated. This mode may also be used to determine the relative proportions of foam and powder that should be employed in subsequent batch or continuous granulation processes involving the same formulation.

In the continuous mode, foam was added to the powder while running the granulator. The foam was homogeneously dispersed in the powder as it was being added. In the batch mode, the entire amount of the foam was placed on top of the powder at any convenient foam flow rate before the high-shear granulator was set into operation.

Table 2 lists the experimental conditions for the comparison of foam granulation of the CR theophylline

Table 1. Formulations used in laboratory-scale granulations.

Ingredients	CR theophylline	CR diphenhydramine HCl	IR acetaminophen
Model drug (%)	41.4	40	69.1
Avicel PH-102 (%)	10.4	15	5.1
Fast-Flo 316 (%)	21.8	–	17.2
METHOCEL K4MP (%)	25.9	–	–
POLYOX (%)	–	30	–
Dicalcium phosphate dihydrate (%)	–	14.5	–
Starch 1500 (%)	–	–	5.1
Ac-Di-Sol (%)	–	–	3.0
Magnesium stearate (%)	0.5	0.5	0.5

Table 2. Experimental conditions for comparison of foam granulation modes for a controlled-release theophylline formulation.

Granulation mode	Level of binder in solution (%)	Rate (g/min)	Total time (s)	Foam addition (g)	Total binder level (%)	Water added (g)
Foam step-batch	1	75	480	600	0.50	594
Foam continuous	1	75	480	600	0.50	594
Foam continuous	1	300	120	600	0.50	594
Foam batch	1	300	120	600	0.50	594

Powder batch size: 1.2 kg; binder: METHOCEL E6PLV; for foamed binder, ''rate'' refers to flow rate of liquid that was foamed.

formulation. Tables 3 and 4 list the experimental conditions for foam granulation of CR diphenhydramine HCl and IR acetaminophen, respectively.

The generated wet masses were wet-milled using a CoMil model 197S grinder (Quadro Engineering, Waterloo, ON, Canada) equipped with a screen with $^3/_8$-in.^{2} (1.27-cm^2) holes (2A-3750037/63) and with an impeller (2A-1607-086L). The grinder was operated at a speed of 1000 rpm. Granulations were dried on trays overnight at 110°F (43°C). Dry milling was accomplished using a CoMil grinder equipped with a round-hole, grater-type screen (2A-062G031-23139) and an impeller (2A-1601-173). The grinder was operated at 1000 rpm.

Pilot-scale Granulation

Formulations

Model drugs included naproxen sodium and acetaminophen. Table 5 lists the formulations for tablets of each drug.

Granulation Method

A 65-L high-shear granulator (Niro, Inc., Columbia, MD) was used with 15-kg charges of powder, operated at a main blade speed of 200 rpm and a chopper speed of 1800 rpm. Foam was added via a 0.5-inch tube through a porthole on the lid of the bowl. The granulator was not equipped with a torque sensor; however, the ''percent load'' on the blade was recorded during granulation. A spray granulation was also performed for comparison with the foam-granulated CR system. Table 6 gives the process details for each experiment. In all cases, the powders were added to the bowl of the granulator and were premixed for 2 minutes prior to addition of binder.

All products were dried in a Glatt WSG-5 (Glatt Air Techniques, Ramsey, NJ) fluid bed drier at the following conditions: 30 min at inlet temperature 60–70°C, air flow rate 125–150 CFM, product end-point 50°C, filter shake interval 45 s/5 s., 10 min at inlet temperature 60°C and product temperature 45°C end-point.

Granulation Testing

The granules were analyzed for density, compressibility (CARR) index (CI), flow, and particle size distribution.[17] The density of a 40-g sample of each granulation was tested using a Vanderkamp tap density tester (model 10700, VanKel Industries, Edison, NJ). A volume measurement was taken before tapping (apparent density) and after 500 taps (tap density).

Table 3. Experimental conditions for comparison of foam granulation modes for a controlled-release diphenhydramine HCl formulation.

Granulation mode	Duration of foam addition	Level of binder in solution (%)	Rate (g/min)	Total time (s)	Foam addition (g)	Total binder level (%)
Foam step-batch	2*30 s	2	150	60	150	0.20
Foam continuous	60 s	2	150	60	150	0.20
Foam batch	60 s	2	150	60	150	0.20

Powder batch size: 1.5 kg; binder: METHOCEL K3PLV; ''2*30 s'' indicates two 30-s additions; ''rate'' refers to flow rate of liquid that was foamed.

Table 4. Experimental conditions for comparison of foam granulation modes for an immediate-release acetaminophen formulation.

Binder solution composition	Granulation mode	Duration of foam addition	Rate (g/min)	Total time (s)	Foam addition (g)	Total binder level (%)
10% PVP	Foam step-batch	5*30	150	150	375	2.50
	Foam continuous		150	150	375	2.50
2% PVP	Foam step-batch	5*30+15	150	165	413	0.55
	Foam continuous		150	165	413	0.55
10% PVP+0.1% SLS	Foam step-batch	5*30+15	150	165	413	2.75
	Foam continuous		150	165	413	2.75
2% PVP+0.1% SLS	Foam step-batch	5*30+15	150	165	413	0.55
	Foam continuous		150	150	375	0.50
10% PVP+2% E3PLV	Foam step-batch	5*30+15	150	165	413	2.75
	Foam continuous		150	165	413	2.75
2% PVP+10% E3PLV	Foam step-batch	5*30+15	150	165	413	0.55
	Foam continuous		150	165	413	0.55
2% E3PLV	Foam step-batch	5*30	150	150	375	0.50
	Foam continuous		150	150	375	0.50

Powder batch size: 1.5 kg; ''5*30+15'' indicates five 30-s additions plus one 15-s addition; ''rate'' refers to flow rate of liquid that was foamed; PVP, polyvinylpyrrolidone; SLS, sodium lauryl sulfate; E3PLV, METHOCEL E3PLV.

The compressibility index was calculated using Eq. 1 below:

$$\% \text{ compressibility} = \frac{100(T-B)}{T} \quad (1)$$

where: T=tapped (packed) density (g/cm^3), B=bulk (apparent) density (g/cm^3).

A 100-g sample of each granulation was shaken for 5 minutes on a RoTap sieve shaker (model B, W.S. Tyler, Gastonia, NC) equipped with a series of five screens and a pan. The amount of material retained on each screen size was measured, and a particle size distribution was calculated.

Tablet Preparation

Tablets were prepared on an instrumented 16-station Manesty Betapress (Thomas Engineering, Inc., Hoffman Estates, IL) modified by D&F Farmaceutica Service (Martin, MI), and equipped with 13/32-inch (10.3 mm) FFBE tooling. The tablet press data acquisition and analysis system was from Binary Applications (Midland, MI). Compressions of 1500 lb (6.7 kN) and 3000 lb (13.4 kN) were used. Tablet weight for production-scale experiments are given in Table 5.

Tablet Physical Properties

Tablets were tested for thickness, hardness, and drug release. The hardness or crushing strength of 20 randomly chosen tablets from each granulation experiment was measured using a Key hardness tester (model HT500, Key International, Englishtown, NJ). Tablet thickness was measured using an Absolute Digimatic caliper (Series No. 500, Mitutoyo Corp., Japan) on 10 tablets of the 20 randomly chosen tablets. The weight of each of the 20 tablets was measured to ensure weight variation was within acceptable USP limits.[18]

Table 5. CR and IR formulations for initial scale-up study.

	mg/tablet	wt %
Controlled-release formulation		
METHOCEL K4MPCR	150	30.0
METHOCEL E6PLV (foamed)	5.0	1.0
Naproxen sodium	220	44.0
FFL-316	122.5	24.5
Magnesium stearate	2.5	0.5
Tablet weight	500	–
Immediate-release formulation		
METHOCEL E6PLV (foamed)	3.9	0.83
Acetaminophen (60-mesh)	325.24	69.2
Ac-Di-Sol	11.75	2.5
Fast-Flo 316	79.43	16.9
Avicel PH-102	23.97	5.1
Starch 1500	23.97	5.1
Magnesium stearate	1.88	0.4
Tablet weight	470	–

Ac-Di-Sol was added post-granulation before addition of the lubricant.

Drug Dissolution

Drug-release testing of six tablet samples from each variable run was performed using a Distek dissolution system (model 2100, Distek, Monmouth Junction, NJ). The testing followed that described in USP-23, Official Monographs, Theophylline Extended-Release Capsules, Test 1 (for products labeled for dosing every 12 h).[18] The USP Apparatus 2 (paddles) method was used at an agitation rate of 50 rpm. Three-prong clips were used to prevent tablets from floating on the surface of the dissolution media during testing. The medium was 900 mL of pH 1.2 simulated gastric fluid (without pepsin) for the first hour; pH 6.0 phosphate buffer thereafter. Data were acquired via a diode array spectrophotometer (model 8452A, Hewlett-Packard Co., Valley Forge, PA). Drug-release profiles were generated at 37.5°C, with detection at 268 nm for theophylline. The acetaminophen assay, per USP-23, used a medium of 900 mL of pH 5.8 phosphate buffer solution. Drug-release profiles were generated at 37.5°C, with detection at 243 nm using Apparatus 2 (paddles) at 50 rpm. The controlled-release naproxen sodium assay, per USP-23 (immediate release tablets monograph), used a medium of 900 mL of 0.1 M phosphate buffer (pH 7.4) solution. Drug-release profiles were generated at 37.5°C, with detection at 332 nm using Apparatus 2 (paddles) at 50 rpm.

RESULTS AND DISCUSSION

Laboratory-scale Experiments

Controlled-Release Theophylline

Visually, all three operational modes produced similar granules from the CR theophylline formulation. No large lumps of overwetted powders and no dry, nonagglomerated powders were observed. Average particle size was less than about 150 μm. In all of the foam operational modes, dust inside the granulator bowl was quickly suppressed.

The qualitative end-point was achieved upon addition of a total of 600 g of foam. In each foam granulation experiment with CR theophylline (Table 2), the powder to be granulated contained the same ingredients in identical proportions (Table 1). The foamed granulation binder was a 1% solution of METHOCEL E6PLV. A control experiment employed a 10% solution of METHOCEL E6PLV as the sprayed granulation binder. Granulation was achieved with less

Table 6. Process information for pilot-scale experiments.

Experiment	Procedure
Acetaminophen, foam step-batch	A 2% solution of cellulose ether (E6PLV) was foamed and added at a rate of 400 g/min in several batches for a total of 9 min addition time. Binder addition was then stopped and the contents of the bowl were mixed for a further 5 min before discharging.
Acetaminophen, foam continuous	Similar to acetaminophen foam step-batch except that the foam was added continuously for 9 min at 400 g/min. Binder addition was then stopped and the contents of the bowl were mixed for a further 5 min before discharging.
Naproxen Na, foam step-batch	Experimental procedures as above with foam added in batches and eventually stopped after 12 min when the powder mass appeared to be acceptable. The contents of the bowl were mixed for a further 2 min.
Naproxen Na, foam continuous	Similar to Naproxen Na foam step-batch but foam addition was continuous at 400 g/min until stopped after 14 min and the contents of the bowl were mixed for a further 2 min.
Naproxen Na, spray	Spray analog of Naproxen Na foam step-batch, i.e., a 2% E6PLV solution was sprayed at 400 g/min into the powder mix.

binder with foam granulation (0.5%) compared to conventional spray granulation (7.3%). Also, foam granulation added 594 g water compared to 788 g water with spray granulation, or 25% less water. Using less water would be an advantage in terms of reducing drying time and granulating water-sensitive formulations. In two of the experiments the addition rate of the foamed binder was quadrupled. Even at this higher rate of addition, control of the granulation process was good, without the overwetting that could occur with spray application.

It is common for the progress of the granulation to be monitored by real-time measurements of the power consumption or torque at the motor driving the main blades. Unfortunately, these values are only indirectly related to granule properties and cannot be used readily in scale-up design.[14,19] Direct measurement of granule properties is complex but could mitigate any need for scale-up studies. Studies on real-time monitoring of granule particle size, coupled with feedback process control[20] for automatic control of the process, have demonstrated the concept but implementation of these techniques is not yet obvious within the industry. In these laboratory experiments, torque was recorded to monitor granulation progress.

The torque/time plot in Fig. 1 is the actual response during the step-batch granulation process for the theophylline formulation. Areas of the curve where the torque returned to baseline represent periods when the rotor blades were stopped (i.e., no torque was experienced on the main blades) to enable visual and manual examination of the progress of the granulation. Figure 2 shows the torque curve for the continuous mode.

Figure 3 shows the torque curve for the batch mode. After as short a time as 5 to 60 s the foam was homogeneously dispersed in the powder. Clearly, it would not be possible to add the total volume of foam in the batch process unless the granulator bowl was of sufficient volume to accommodate the powders and the foam. In such cases, the concentration of polymer in the foamed solution may be increased or a portion of the foam may be added in batch mode and the remainder added as required by any of the three methods once the initial foam portion was incorporated within the powder mass.

Drug-release profiles of tablets prepared from the granulated materials from each of the experiments are shown in Fig. 4. The drug-release profiles show similarity when comparing different foamed binder delivery rates and different foam application techniques. In the laboratory, the authors have repeatedly observed minimal impact of delivery rate or method of

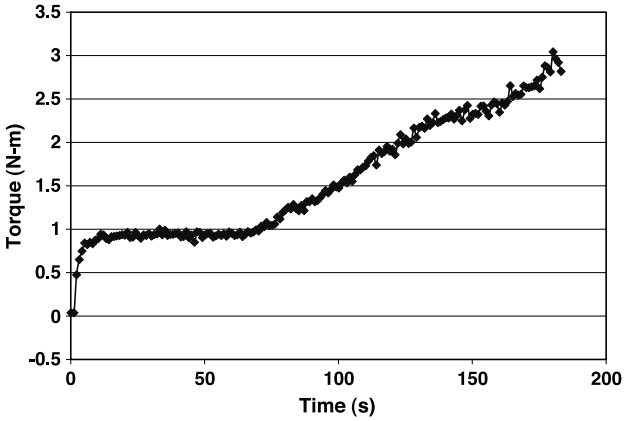

Figure 2. Torque curve for foam granulation of CR theophylline formulation, continuous mode.

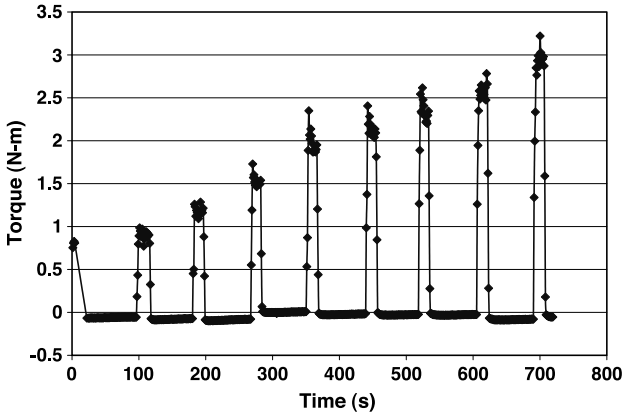

Figure 1. Torque curve for foam granulation of CR theophylline formulation, step-batch mode.

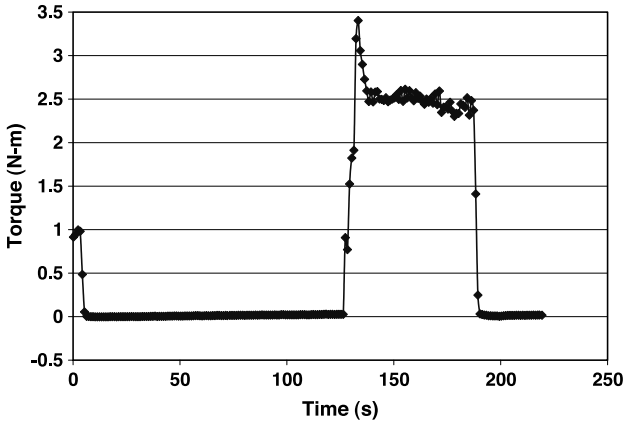

Figure 3. Torque curve for foam granulation of CR theophylline formulation, batch mode.

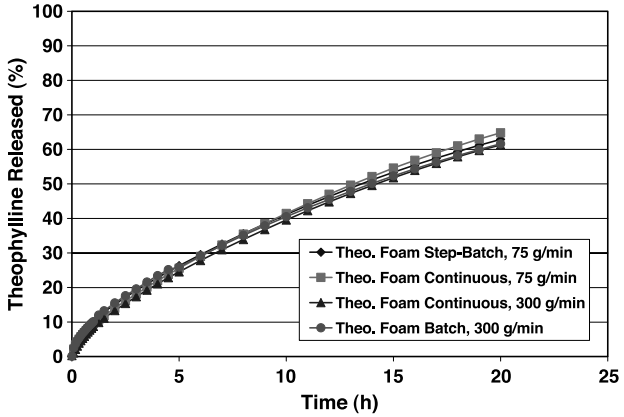

Figure 4. Drug-release profiles of tablets prepared by foam granulations of CR theophylline.

addition of foamed polymeric binders on drug release. The foam appears to uniformly distribute the water-binder system throughout the moving powder bed during high-shear granulation.

Controlled-Release Diphenhydramine HCl

From previous experience, this formulation has been difficult to wet granulate by conventional spray granulation. However, granulation proceeded easily using all three modes of foam addition of binder. The extreme water solubility of diphenhydramine HCl (1 g/1 cm^3 water) and the water sensitivity of the polyethylene oxide did not cause any operational problems. This was a range-finding experiment; no tablet properties or drug-release profiles were measured.

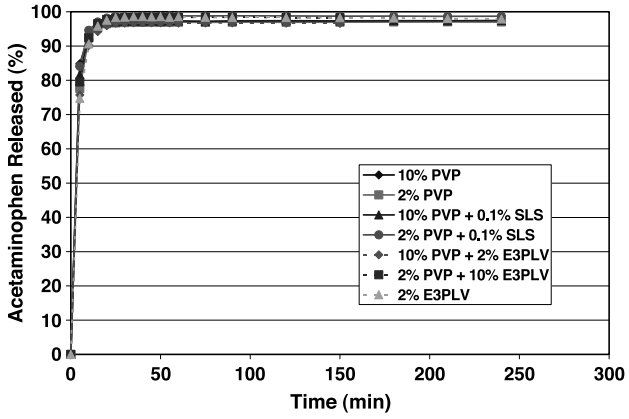

Figure 5. Drug-release profiles of tablets prepared by continuous foam granulations of IR acetaminophen with varying binder composition and level.

Immediate-Release Acetaminophen with Polyvinylpyrrolidone Binder

IR acetaminophen formulations were granulated as previously listed in Table 4. The objective of this series of experiments was to demonstrate the applicability of foam granulation technology to formulations that involve binders that are inherently not surface-active. A 3% solution of polyvinylpyrrolidone (PVP, Plasdone 29/32) has a surface tension[12] of 68 mNm^{-1} at 25°C; a 3% solution of cellulose ether (METHOCEL E5PLV) has a surface tension of 48 mNm^{-1} at 25°C. Considering that water has a surface tension of 72 mNm^{-1} at 25°C, it is apparent that PVP is significantly less surface-active than the cellulose ether. In effect, PVP stabilizes foams simply by viscosifying the lamellar phase, whereas cellulose ethers stabilize foam by reduction of interfacial tension and by viscosifying the lamellar phase. In some of the experiments, surfactant (sodium lauryl sulfate, SLS) or cellulose ether (METHOCEL E3PLV) was added to PVP to decrease interfacial tension. Also, in some experiments, cellulose ether (METHOCEL E3PLV) was used alone as the binder for comparison. For each rate and formulation, experiments were conducted initially by the step-batch mode of foam granulating and then by the continuous-addition mode.

Drug-release profiles for tablets prepared in the continuous mode experiments are shown in Fig. 5; all formulations gave similar releases. The release profiles were within USP-23 acetaminophen monograph specifications of not less than 80% acetaminophen released in 30 minutes.

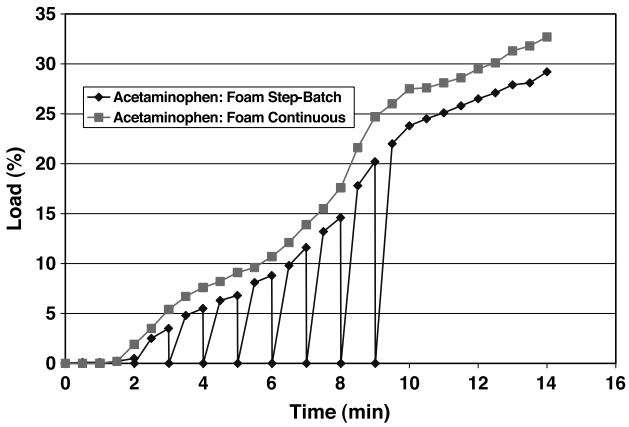

Figure 6. Progress of 15-kg-scale foam granulations of IR acetaminophen formulation.

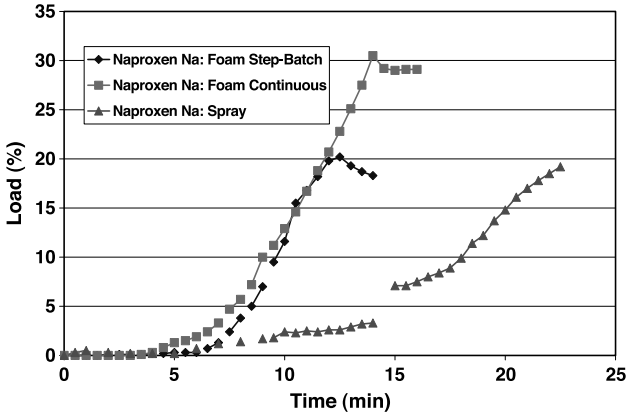

Figure 7. Progress of 20-kg scale foam granulation of CR naproxen Na.

Pilot-scale Experiments

Granulation Process

Progress of the IR acetaminophen granulations was monitored as illustrated in Fig. 6. It was interesting to note the similarity between the load curves of the step-batch and the continuous process. After 9 minutes of foam addition, continued agitation of the powder mass resulted in a steady increase of the load on the blade. It is unknown how high a blade load could have been achieved with prolonged mixing. We arbitrarily decided to cease mixing 5 minutes after the end of foam addition.

Progress of the CR naproxen sodium granulations was monitored as illustrated in Fig. 7. The load curve for the step-batch process reached a maximum of approximately 20% while foam was being pumped into the system during the first 12 minutes and did not increase in value during the 2 minutes of mixing during which foam addition was not taking place. This is taken to illustrate that there was efficient real-time mixing of the foam while it was being pumped and that no ''free'' foam was left to be mixed during the last 2 minutes. This behavior contrasts with the curves for the IR formulations, Fig. 6.

To study the effects of increasing the ''wetness'' of the powder mass, a continuous foam addition was performed in which we added more foam than had been added during the initial step-batch experiment. As expected, the load value was increased, as shown in Fig. 7. Again, load values did not increase during the post-addition period of mixing.

In the spray process, binder was sprayed to a known weight of addition, spray was then switched off, and the granulator was allowed to continue mixing for a further 2.5 minutes. During the experiment, binder was pumped for 20 minutes, after which it is clearly seen in Fig. 7 that blade load continued to increase. This has been interpreted as indicative that addition of binder as spray was less efficient than addition of binder as foam.

If an increasing blade load is truly indicative of a system that continues to mix once binder addition has been stopped, comparison of Figs. 6 and 7 illustrate that certain formulations mixed very efficiently with foam while other foam-granulated formulations may not have mixed as well. An alternative explanation may be that the IR formulations, Fig. 6, were not optimized with the quantity of foam that was added. It is possible that more foamed binder could have been added without over-wetting the powder mass, but we were reluctant to ''push'' the system to its limits. If more foam had been added, it may be that blade load would not have continued to climb upon additional mixing with addition of foam switched off. This is an aspect of high-shear, wet granulation with foam that merits further study.

Certainly the observations with sprayed binder addition, Fig. 7, are in agreement with observations[11] that efficient use of viscous binder is dependent upon mechanical energy input. The increasing blade load without additional binder, as mixing continues, is a clear demonstration of mechanical energy improving the homogeneity of the powder-binder mixture.

Table 7. Water and binder levels in scale-up experiments.

Experiment	Water in granulated product (%)	METHOCEL E6PLV in granulated product (%)
Acetaminophen, foam step-batch	19.4	0.4
Acetaminophen, foam continuous	19.4	0.4
Naproxen Na, foam step-batch	24.2	0.5
Naproxen Na, foam continuous	27.2	0.6
Naproxen Na, spray	46.0	1.0

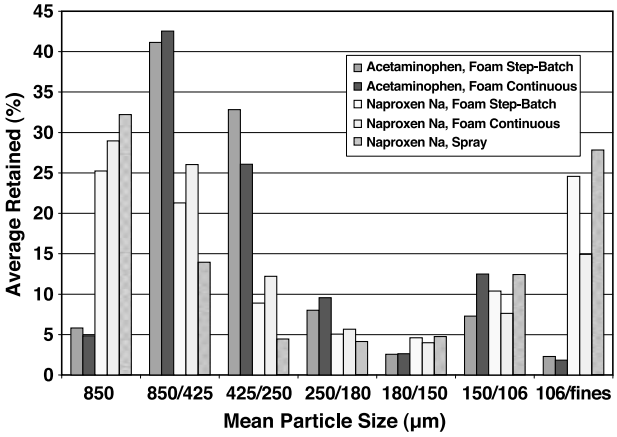

Figure 8. Particle size distribution from scale-up experiments.

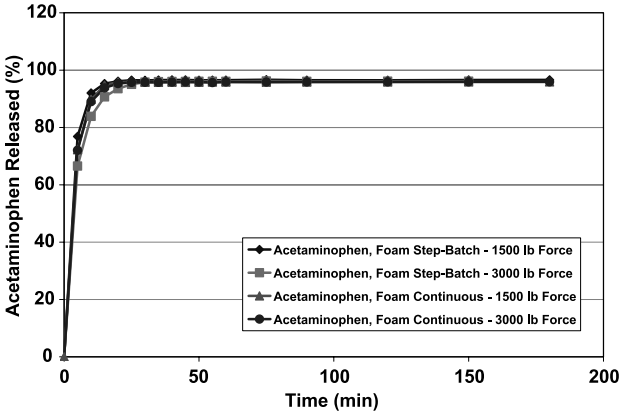

Figure 9. Drug-release profiles for scale-up experiments with IR acetaminophen.

Granulate and Tablet Properties

Table 7 shows the water and binder levels resulting from the scale-up experiments. The amount of water required to properly wet the powder mass using a conventional spray technique was significantly greater than that required using the foam technique, possibly due to the higher surface area and volume of the foam. Typically, it requires less water to wet granulate when using foamed binders than compared to sprayed binders.

Particle size distributions from both sets of experiments are shown in Fig. 8. For each set of experiments, a similar distribution of granules was obtained regardless of the method of granulation. Tablet physical properties are listed in Table 8; results are presented for tablets prepared at two compression forces, 1500 and 3000 lb. The 1500-lb compression was possibly too low for these tablets. However, all testing results are included for informational purposes. The tablet testing results showed similarity within both sets of experiments. There were no significant differences within each set of experiments (acetaminophen and naproxen sodium) when comparing methods of granulation.

Drug Dissolution

In-vitro drug-release profiles of the IR formulations were measured, Fig. 9, for tablets prepared at two different compression forces; the release profiles were within USP-23 acetaminophen monograph specifications of not less than 80% acetaminophen released in 30 minutes.

Drug-release profiles for the CR formulations are shown in Fig. 10, for tablets prepared at two different

Table 8. Processing of foam scale-up experiments—tablet physicals.

Experiment	Avg mean compression force	Hardness		Thickness		Weight variation	
		Mean (SCU)	Std. dev.	Mean (mm)	Std. dev.	Mean (mg)	Std. dev.
Acetaminophen,	1406	4	0.5	5.129	0.03	468.795	6.02
foam step-batch	2858	8.5	0.6	4.816	0.02	467.975	4.02
Acetaminophen,	1512	3.7	0.6	5.039	0.02	463.345	1.55
foam continuous	3072	8.6	0.7	4.726	0.02	465.95	3.97
Naproxen Na,	1639	7.8	1.2	5.666	0.05	494.75	5.31
foam step-batch	2949	19.4	2	5.1666	0.03	500.665	8.02
Naproxen Na,	1436	9.8	1.1	5.49	0.02	496.285	5.51
foam continuous	3168	22.1	2.1	4.891	0.05	492.345	7.33
Naproxen Na, spray	1512	9.4	1.2	5.436	0.02	504.28	5.30
	2610	20	1.2	5.059	0.02	506.015	3.87

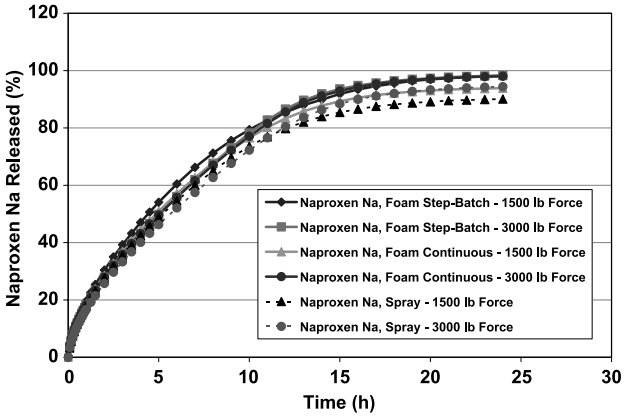

Figure 10. Drug-release profiles for scale-up experiments with CR naproxen Na.

compression forces compared to spray application. Drug release was only minimally affected by the method of granulation and the level of applied force used during tablet preparation. In addition, a significant advantage of using foamed polymeric binders rather than a sprayed liquid system is the elimination of nozzles. Whereas convention spray systems require nozzles to properly deliver the binder system, foam granulation delivers the binder system via a tube to the high shear granulator through the spray port opening. With foamed-binder addition, formulation scientists and manufacturing personnel would no longer have to address nozzle selection criteria, nozzle spray patterns, liquid droplet size distribution, solution viscosity, atomization air, and other variables associated with nozzle delivery of binder solutions. The physical properties of foam lend themselves ideally to high-shear granulation.

GENERAL DISCUSSION

Foam Quality and Foam-Particle Interaction

A useful expression of foam properties is the term ''Foam Quality'' (FQ) that is given in the following equation. V refers to the volume as designated by subscript for liquid or gas.

$$FQ = \left(\frac{V_{GAS}}{V_{GAS} - V_{LIQUID}}\right) \times 100$$

A foam of FQ < 70 is typically considered to be a wet foam and will exhibit a low rheological yield stress and will tend to flow like a liquid. A foam of FQ > 70 has a high gas-to-liquid ratio and a comparatively high rheological yield stress. As a consequence of the latter, high-quality foams show solid-like flow properties below their yield stress. Such foams tend to flow in pipes by wall slippage.

Foam density, ρ_F, is readily calculated by the following equation[21] in which ρ_L is the density of the liquid phase and V refers to the volume as designated by subscript for liquid or foam.

$$\rho_F = \rho_L\left(\frac{V_L}{V_F}\right)$$

Foams are not inherently limited in composition to only an aqueous phase and a gaseous phase. We have prepared multiphase foams but we have not yet evaluated this aspect sufficiently for publication. It is commonly known that nonaqueous liquids[22] and solids[23] are capable of stabilizing foams, and we will exploit these aspects in future applications of foam technology.

Cellulose ethers are effective foam stabilizers, enabling preparation of foams of various stabilities. The concentration, molecular weight, and substitution type of the polymer that is in solution can be varied. Additionally, we can vary the nature of the aqueous phase and the foam quality. These options allow great flexibility, but obviously foam that is either too stable or insufficiently stable would not be desirable. What determines the required stability? The required stability is highly dependent on the process, but certain general guidelines can be given. Viscous solutions, 150–300 cP, will produce highly elastic foams that have a high yield stress; such foams will have a very low tendency to spread. These foams are the most difficult to produce and often have the lowest foam quality. Low viscosity solutions, 3–100 cP, are easy to foam and can result in very high quality foams of low density. For example, foam density of 0.05 g/cm^3 is readily achievable from a 10% solution of METHOCEL E3P. At the end of the granulation process, if foam remains in the materials that are being processed, the foam is too stable. The options are either to increase the mechanical energy of mixing, mix for a longer period of time, or use a less stable foam.

In the foams of this study, liquid is the continuous phase, functioning as the lamellae of the bubbles. Conversely, liquid is discontinuous in sprayed liquids. Air is commonly the continuous phase but there is no inherent association between the spray droplets and the air as there is with the foam analog. This phase-inverted relationship between foams and sprays has a

profound effect on their liquid surface areas. Let us simplify our calculations by assuming that we generate only noninteracting spherical bubbles and spherical droplets. If we consider a liquid of density 1 g/cm^3 and we generate monodisperse spray droplets of 200-μm radius, the surface area per gram of liquid is approximately 150 cm^2. This is regardless of the liquid-to-air ratio. In foam of the same liquid, the liquid-to-air ratio has enormous significance, e.g., at a 9:1 ratio of air to liquid, assuming monodisperse bubbles of radius 200 μm, the surface area per gram of liquid is nine times that of the sprayed system, i.e., 1350 cm^2. We can calculate[21] the lamella thickness, h, from the simple relationship, $h = 2V_L/A$, where A is the surface area of the liquid. In this example, the lamella thickness is approximately 1.5 μm. By simply foaming the liquid we have approached nanoscale structure within the foam.

In sprayed systems, the spray droplets are of the same size range as the powders to be granulated. Similarly with foamed systems, the bubbles are of the same size range as the powders. A significant difference between these two cases is that impingement of a spray droplet onto a particle can be viewed as an interaction between two three-dimensional species. With foamed systems, there may be value in considering the initial encounter of a particle and a bubble as the interaction between a three-dimensional particle and a two-dimensional lamella. It is not immediately apparent how valid this concept is in light of the fact that lamellae interact with each other at adjacent plateau borders that are three-dimensional features of all foams. These aspects of foam-particle interactions have not been reported in the literature as far as we have been able to determine.

Mechanism of Foam Granulation

Discussion of wet granulation[11,15] commonly identifies three groups of interacting events that influence the properties of the granular product. These are granule nucleation and binder distribution, granule consolidation and growth, and granule attrition and breakage. We propose here a working hypothesis for the mechanism of foam granulation of powders. Clearly there are numerous details of this mechanism that remain to be studied. It is hoped that once the pharmaceutical industry and academia become more widely aware of this new process that it will be seen as a fertile area for R&D.

The mechanism illustrated in Fig. 11 is derived from theories that were developed to explain the use of foamed fluids in enhanced oil-recovery processes.[24]

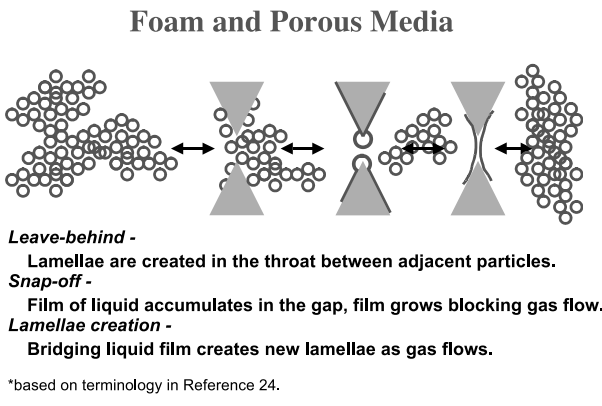

Figure 11. Mechanism of foam generation.

Figure 11 is complex due to the fact that it illustrates a static cross-section of a dynamic three-dimensional process. The use of double-headed arrows within the figure is to emphasize that the process may be considered to proceed in either direction. The illustration also serves to explain the flow of foam through porous media, such as powders, and the flow of powders through foam. A critical element is that foams are able to flow through porous media by a ''breaking and remaking'' process. In such a process, foam bubbles that burst may create bridging lamellae between powder particles that can act as bubble regeneration points as the lamellae are contacted by free gas or foam. This is analogous to blowing a bubble from a ring that has been dipped into a soap solution, catching the bubble on another ring and then blowing further bubbles from the catching ring.

On the contrary, consider a spray droplet that encounters a porous solid surface, such as a powder mass. The droplet cannot travel further than the initial point of contact unless collision with another powder particle causes transfer of some, or all, of the droplet onto the colliding particle. The more common fate of the spray droplet is for it to be absorbed by the surface that it impinged upon or for the droplet to penetrate into the powder mass by capillary action and mechanical dispersion.

A property of foams that appears to influence the granulation mechanism is the ''spread-to-soak'' ratio. This property has been exploited in the textile industry[25] for treatment of fabrics with functional liquids. The driving force to use foams for treating textiles is the need to conserve energy by avoiding water uptake by fabrics and thereby reduce the energy required to dry the fabrics. Foams are described[26] as having the property of ''low wet pickup;'' quite simply foams replace water that would normally be used in the

process with air. Turner[26] states that ''thin fabrics with high porosity are best treated with dense foam, while heavy and tightly constructed styles are best treated with light foam; the ability of the foam to collapse into the fabric as it is applied is most important.'' Another crucial observation by Turner[26] is ''when a bubble touches something dry, it will burst and wet the surface of whatever it touches. However, when a bubble touches a wet surface, particularly if wet with its own chemical system, it will slide along that wet surface until it reaches a dry section, and then collapse. In this manner it is possible for foam to penetrate dense materials.'' Differences between treating a web of fabric and treating an agitated powder mass are obvious but the same concepts of wet pick-up, foam penetration, and foam collapse are applicable.

By combining the above aspects into a proposed mechanism for foam granulation, we have arrived at a hypothesis as illustrated in Fig. 12. The mechanism emphasizes the ability of foam to spread rather than to soak; particles that are initially noncoated become surface-coated by the spreading foam. There is no doubt that liquid from foam will also be absorbed into the powder mass to some extent. Subsequent stages, in which the powder particles become agglomerated into a certain particle size distribution, are no different from the sprayed process.

Figure 13 shows a micrograph of a foamed solution, dyed to enhance contrast, and illustrates the enormous surface area that is created by the foaming process. Useful foams, in the current context, typically have a range of bubble diameters that average approximately 100 μm. The lamellae that define these bubbles are typically less than 10 μm thick. This is not clearly visible in Fig. 13 because of poor optics and the required optical dynamic range, but it is apparent that the lamellae are at least one order of magnitude smaller than the bubbles.

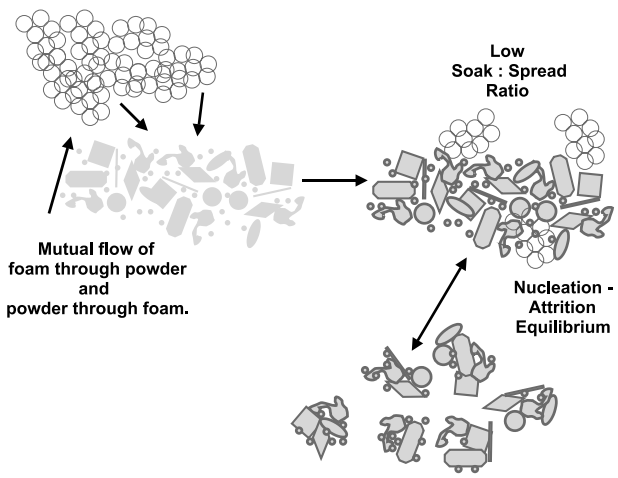

Figure 12. Nucleation process in foam granulation.

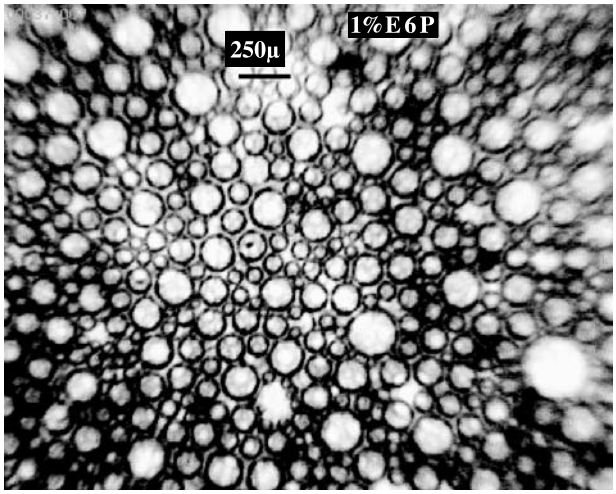

Figure 13. Bubble structure of flowing foam of 1% METHOCEL E6P solution.

CONCLUSIONS

A new granulation process using foamed aqueous binders has been discovered for wet granulation of drug formulations. In laboratory experiments (1.2–1.5 kg), foamed aqueous binders were successfully used to granulate controlled-release and immediate-release drug formulations, including one formulation that is highly sensitive to water addition and one formulation using binders with low surface activity. In general, the foamed binder experiments required less binder and less water than comparable spray binder application while achieving similar granulate properties. Even at high application rates, control of foam granulation was good. There were no detrimental effects on drug dissolution properties.

Scale-up experiments (15 kg) showed that both a controlled-release and an immediate-release formulation using foamed binders could be successfully scaled up. The granulation process was very controllable, granulate and tablet properties were acceptable, and drug dissolution was on-target.

This paper also presents a working hypothesis of the mechanism by which foam granulation operates. These initial experiments indicate that the potential advantages of this new process over spray delivery in wet granulation include improved distribution of binders

and the granulation liquids throughout the powder mass, improved control of liquid addition without the need for nozzles, reduction in manufacturing time, faster application rates, unique 1-step (batch) process, and possibly less binder required for IR and CR formulations. In our experiments we were able to foam several commonly encountered pharmaceutical binders.

Foam granulation merits further refinement and study. Application of this technique by the pharmaceutical industry and other industries will be a function of the inherent conservatism and regulatory controls within the industry.

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