

Comparing Drug Layering and Direct Pelletization Processes

The extended-release performance of drug-loaded pellets manufactured by two methods, drug layering and direct pelletization, was compared.

Pharmaceutical
Technology

Mar 02, 2014

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Pharmaceutical Technology



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Common controlled-release product designs include the manufacture of polymer-coated multiparticulates. A crucial aspect to the success of this method is to create drug-containing multiparticulates (i.e., drug pellets) that are spherical, consistent in particle size, and possess smooth and regular surfaces. If these three attributes are achieved, a polymer layer of a consistent thickness can be applied to the surface of the pellets. Consistent thickness of this polymer membrane will ensure consistent and reproducible drug dissolution from unit to unit.

Several techniques are available to create pellets that contain uniform drug distributed among them. This study explores two of these methods: drug layering and direct pelletization.

Drug layering involves depositing the drug on the surface of a substrate. The most common way of depositing the drug on the substrate is by using air-suspension coating. The drug first must be dispersed in a liquid carrier, either water or an organic solvent. This dispersion is then sprayed onto the substrate (usually sugar or microcrystalline cellulose [MCC] spheres) in a fluid-bed apparatus, traditionally a Wurster Column (Wurster HS, Glatt). In the Wurster, the substrate particles are fluidized and suspended by heated and conditioned air. One or several nozzles atomize and spray the drug dispersion onto the substrate. The heated and conditioned air then evaporates the liquid carrier, leaving the drug deposited on the substrate.

A proprietary, direct-pelletization method (CPS Pelletization Technology, Glatt) requires the drug to be mixed with an excipient, such as MCC and water, in a mixer to produce a damp mass. The damp mass is processed into spheres in the CPS fluid-bed unit. In the CPS unit, the loose agglomerates in the damp mass are densified and spheronized by an orbital motion created by air suspension and other mechanical means. During the densification process, small, uniform spheres are initially produced. With the application of these mechanical forces and, in some cases, additional water, the smaller spheres coalesce and form larger, smooth spheres in a stepwise fashion. When the desired particle size is achieved, the process is stopped. The resulting wet spheres are then dried in a fluid-bed dryer.

This study compares the yields and process times for each method as well as the physical properties of the resulting pellets. Both pellet types were coated with a controlled-release polymer using the same process and formula to compare dissolution behavior and determine if differences in makeup of the pellet influence dissolution. Finally, a pellet with the entire amount of drug concentrated on the surface was evaluated to see if it exhibited faster dissolution than a pellet that has the drug uniformly dispersed throughout.

Materials and formulation

Materials used for this study were: propranolol hydrochloride (HCl), USP (Ipca Laboratories), MCC (Vivapur PH-105, JRS Pharma), MCC pellets with a nominal diameter of 700 μm (Cellets 700, Glatt Air Techniques), polyvinyl-alcohol-based coating (Opadry Clear, Colorcon), ethylcellulose polymer (Ethocel Standard 10 Premium, Dow), dibutyl sebacate (Vertellus Specialties), Ethanol 200 (Spectrum Chemical).

To remove the variability of materials from this study, the same formulation was applied to make both types of pellets (see **Table I**). The formulation consisted mainly of propranolol HCl and MCC in both pellets. The MCC in the drug-layered pellets was in the form of Cellets 700, and the MCC used in the CPS-pelletizing method was in powder form. To ensure that the propranolol would adhere to the MCC spheres, a small amount of binder (Opadry Clear) was needed in the drug-layering process. Consequently, the ratio of MCC to the active is slightly reduced in the drug-layering formula (i.e., for the Wurster HS).

Table I: Drug pellet formulation.

	Drug layering	Direct pelletization
Inredient		

	Amount/unit (mg)	Amount/batch (g)	Amount/unit (mg)	Amount/batch (g)
Propranolol hydrochloride	60	1125	60	1200.0
Microcrystalline cellulose	330	6187.5	340	6800.0
Binder	10	187.5	–	–
Water	–	5981.3	–	7800.0
Total	400	7500.0	400	8000.0

Each pellet was coated with a formulation of ethylcellulose (Ethocel Standard 10 Premium Ethylcellulose Polymer, Dow) dissolved in ethanol, using dibutyl sebecate as a plasticizer (see **Table II**).

Table II: Extended-release formulation.		
Ingredient	Coating (to 8% weight gain)	
	Amount/unit (mg)	Amount/batch (g)
Propranolol hydrochloride pellets	400	1500.0
Ethylcellulose polymer	28.8	107.0
Dibutyl sebecate	3.2	12.0
Ethyl alcohol	–	1071.0
Total	432	1619.0

Methods

Drug milling. Propranolol HCl was first milled by passing through a Fitzmill (hammers forward, high speed, screen 1536-0040A) twice to reduce the particle size to less than 50 μm . The milled form of the drug was used in both the Wurster drug-layering process as well as the CPS direct-pelletization process.

Drug-layering process. Propranolol HCl drug-layered pellets were made using a Glatt GPCG-5 7" Wurster HS at Glatt Air Techniques. The drug dispersion was prepared by hydrating Opadry Clear in water and mixed until a clear dispersion was obtained. The milled propranolol HCl was then added while mixing until a lump-free dispersion was formed. This dispersion was mixed throughout the layering process to ensure the solids remained in suspension. The dispersion was applied to MCC spheres in the 7" Wurster. The resulting drug layered-pellet particle size D50 was approximately 880 μm .

Direct-pelletization process.

Propranolol HCl drug CPS pellets were made using a Glatt CPS-3 Processor at Glatt Air Techniques. The milled propranolol HCl and MCC were mixed in a mixer (Glatt VG-25) under low-shear conditions. Water was added to this mixture to obtain a moisture level between 25 and 30%. The wetted mixture was divided into three equal parts. Each part was processed in the CPS-3 unit to create drug pellets with a D50 of approximately 900 μm . The wet, formed particles were then dried in a Glatt GPCG-1 fluid-bed processor.

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Extended-release coating process. Both types of drug pellets were coated with ethylcellulose polymer in ethanol, with dibutyl sebecate as a plasticizer, using a Glatt GPCG-2 7" Wurster at Colorcon. The coating solution was prepared by dissolving the Ethocel in ethanol and mixed until a clear solution was formed. The dibutyl sebecate was then added and mixed for one hour. This coating solution was applied in the 7" Wurster. During the coating process, samples were removed at 4, 6, and 8% weight gains to evaluate for dissolution.

Dissolution method. The dissolution of each sample taken was performed using the following method (internal standard method, Colorcon):

Apparatus: USP I (basket)
Dissolution medium: USP purified water
Media volume: 1000 mL
Media temperature: 37.3 °C

Speed: 100 rpm
 Sample size: 1 g
 Vessels: 3
 UV wavelength: 289 nm
 Time points: 30, 60, 90, 120, 180, 240, 360, 480, 600, and 720 min.

Film thickness determination. Film thickness was visually determined using scanning electron micrographs (SEMs) of the cross-section of coated pellets. The film thickness was compared against a known length shown on the key at the bottom of the micrograph.

Particle-size distribution. Samples were analyzed by dynamic image analysis (Camsizer, Retsch Technologies).

Results and discussion

Table III summarizes the characteristics of each process and the resulting drug-loaded pellets, and **Figure 1** compares SEMs of the pellets. Although there are more process steps in the CPS Direct Pelletization process, the overall manufacturing time was shorter than that for the Wurster drug-layering process by approximately 15%. Each process had similar yields, with the drug-layered pellets being slightly better.

Table III: Drug pellet process comparison.		
Pellet type	Direct pelletization	Drug layering
Process time	Milling: 60 min	Milling: 60 min
	Pre-wetting (X2) : 40 min	Suspension preparation: 130 min
	Pelletizing (X6) : 240 min	Layering, drying: 310 min
	Drying (X2): 90 min	
TOTAL	430 min	500 min
Throughput	1.12 kg/hr	0.9 kg/hr
Particle size		
D10(μm)	757	793
D50(μm)	906	883
D90(μm)	1129	1006
Yield	95.7%	97.5%

The particle size of the MCC substrate (Cellets) used in the Wurster process was selected to target final drug-layered particles of approximately 1 mm in diameter. After the drug-layering process was carried out, particle size analysis showed the median particle diameter (D50) to be 883 μm . The CPS Direct Pelletization process parameters were manipulated to produce pellets with a D50 approximating the 883 μm D50 achieved in the drug-layered batch. The final, dried CPS pellets' D50 was 906 μm , which is within 2.6% of the D50 of the drug-layered pellets. Overall, each technique produced pellets that were round and smooth with similar particle-size distributions.

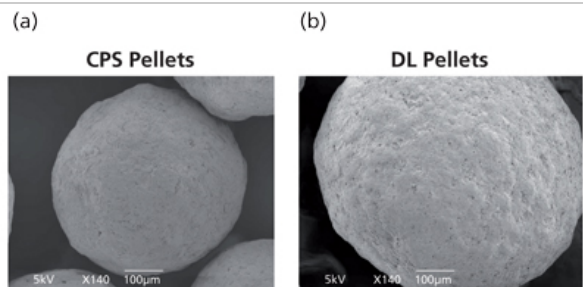


Figure 1: Scanning electron microscope images of pellets made using (a) direct pelletization with the CPS method and (b) drug layering (DL).

Since the D50 and distribution were similar, the surface area-to-weight ratio could also be considered similar. This similarity is important, since the subsequent polymer-coating thickness will be estimated based on weight gain. If the surface area-to-weight ratio of two particle sets is similar, it can be assumed that the resulting coating

thickness will also be similar based on weight gain.

When each pellet type was coated with ethylcellulose, samples were withdrawn at 4, 6, and 8% weight gains. Particles from each sample were carefully split in half and SEMs of each split particle were taken. From these micrographs, it was determined that the coating thickness was about the same for both pellet types at each weight gain (see **Figures 2, 3, and 4**).

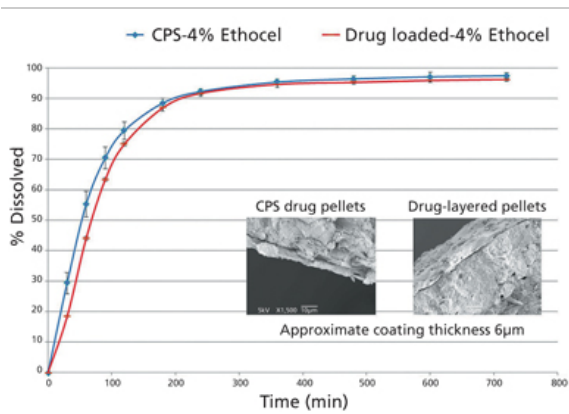


Figure 2: Dissolution, 4% weight gain, 6 µm film thickness.

The dissolution of both pellet types was compared in **Figures 2, 3, and 4** at weight gains of 4, 6 and 8% respectively. As the weight gain increases from 4 to 6 to 8%, the dissolution rate of the CPS pellets is slower than that of the drug-layered pellets. This result is most likely due to the fact that in the CPS pellets, the drug must migrate through the MCC because it is dispersed throughout the pellet. The drug is only on the surface of the drug-layered pellets, so it can release completely through the polymer film. It should be noted that in the case of the 4% weight gain, both pellets exhibited almost the same dissolution profile with over 80% of the drug released in approximately 2.5 h. In reality, these dissolution rates might not be desirable for some controlled-release applications, but the data is presented here for comparison purposes to the other weight gains.

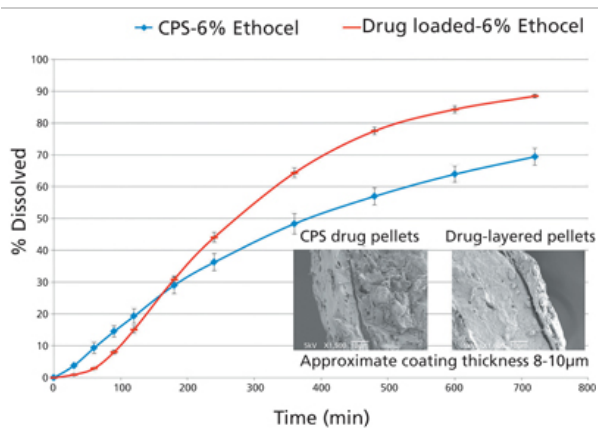


Figure 3: Dissolution, 6% weight gain, 8-10 µm film thickness.

It is also interesting that the shape of the dissolution curves change as well. The drug-layered pellets exhibit a delay in release while the CPS pellets begin releasing immediately. This result can be explained by the tendency of MCC to swell. In the CPS pellets, when the dissolution media diffuses through the polymer, it contacts MCC as well as drug. As the MCC absorbs the dissolution media, it begins to swell and can create fractures in the polymer film, allowing the drug to diffuse immediately. Subsequently, the dissolution rate slows due to a low concentration gradient at the surface of the pellet. The release of the drug is therefore controlled by its migration through the MCC matrix.

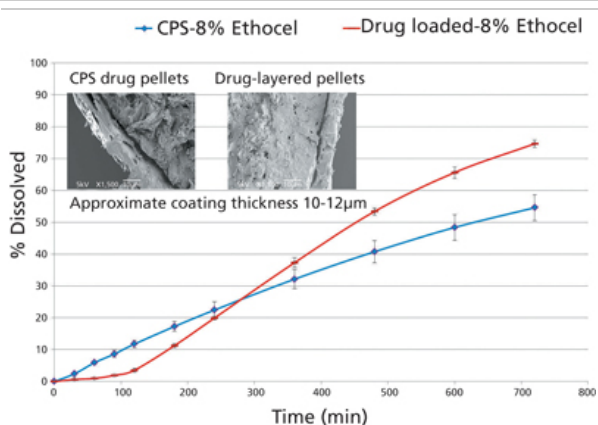


Figure 4: Dissolution, 8% weight gain, 10-12 µm film thickness.

In the drug-layered pellets, the dissolution media diffuses through the polymer film to reach the drug layer. The drug then must be dissolved and migrate back through the film into the bulk dissolution media. This causes the delay in dissolution as seen in **Figures 3 and 4**. The overall rate is then controlled by the higher concentration gradient and the diffusion mechanism and the high concentration of drug on the pellet surface.

Conclusion

The data show that processing times for direct pelletization using CPS technology are slightly better than traditional suspension layering using a Wurster. With further optimization and development of the CPS process, shorter production times could easily be realized.

Even though the median particle diameter of both pellet types was similar, the CPS pellet particle-size distribution is slightly wider than that of the drug-layered pellets. Since multiple portions of CPS pellets are combined to make a batch, it is possible that the wider distribution is due to the slightly different mean particle size of each portion. With further optimization, this distribution could be reduced.

When coated with ethylcellulose to the same weight gains, CPS pellets exhibit a slower dissolution rate than drug-layered pellets. Therefore, less coating needs to be applied to a CPS pellet than to a drug-layered pellet to achieve a target dissolution rate. The shape of the coated CPS-pellet dissolution curve, however, is different from the coated drug-layered pellet dissolution curve. The lack of a delay in dissolution may be desired, depending on the pharmacokinetics of the drug.

Depending on the required performance of the final dosage form, each method described has its advantages to a formulator. For products that require a delay in release for bioavailability, the traditional drug layering and coating via Wurster bottom spray may be desirable. If a zero-order release is required, pellets manufactured using CPS could be selected.

Additional studies should be performed to evaluate how drug concentration in each pellet type affects dissolution and overall product performance. In terms of process times, it is expected that the drug-layered process times would increase with increased drug concentration, while the process time for CPS would remain unchanged. Further characterization of the pellet physical properties, as well as content uniformity can also be evaluated.

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