Case Study:
Conical Rotor Technology

Discussion Of Processes Which Utilize Conical Rotor Technology

- ✓ *Spherical Granulation*
- ✓ *Powder Layering of Actives or Polymers*
- ✓ *Solution/Suspension Application of Actives or Polymers*

Introduction...

The purpose of these study was to develop and introduce several novel processing methods which can be done with the GRANUREX® conical rotor technology. These methods include spherical granulation, powder layering, and solution/suspension coating.

The Solution...

The GRANUREX® (GXR) conical rotor technology has improved many aspects over conventional flat rotor processing. First, the gap or slit between the rotor and the stator is fixed and is very small and precise, which allows for superior control and high velocity of very low volumes of process airflow. The ability of the conical rotors to control and distribute very low process airflow volumes allows for greater processability of micronized powders, which are essential for creating small, uniform multi-particulate dosage forms.

The conical shape of the rotor orders the flow of the product past the spray gun, allows for larger batch sizes than conventional flat rotors, and also creates superior mixing than what is possible with the flat rotors. Ball mounted spray and powder guns which are located in the product bed provide efficient spray transfer onto the product with minimal spray drying effects.

These improvements have made conical rotor technology a superior option for the creation of multi-particulate dosage forms.

The Conclusion...

FREUND's studies have shown that the conical rotor processes are viable alternatives to today's conventional granulation and coating methods.

The key advantages of the conical rotor seen with all processes in the studies are significantly decreased process times and reduced material requirements (organic solvents, glidants, etc.) which can result in lower costs and greater productivity.

Other advantages to the conical rotor system include high process yields, high content uniformity, the unique ability to create multi-layer multi-particulates very quickly, and the ability to apply functional polymers in dry form or via traditional solution/suspension spray with great speed and efficiency.

GXR-35

Highlights

- ✓ Significantly Decreased Process Times
- ✓ Material Reduction (organic solvents, glidants, etc.)
- ✓ Increases Spray Rate
- ✓ High Process Yields
- ✓ Lower Cost

Who We Are...

For 60 years, FREUND has been a world-class custom granulation and coating equipment solution provider prepared to satisfy your requirements on a global scale.

We offer Fluid Beds, Roll Compaction, High Shear Granulators, Tablet Coaters, Spray Dryers and Powder Handling.

Our Mission:
Creating Essential Technologies For a Brighter Tomorrow

Method 1: Spherical Granulation

Spherical granulation resembles a hybrid process between top spray granulation and high shear granulation. Starting with a micronized API in the conical rotor, a binder solution is sprayed onto the powder to form granules. The spinning rotor imparts force onto the powder, forming a spherically-shaped granule.

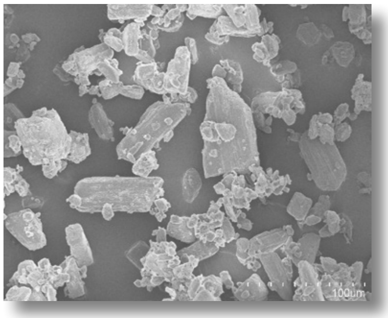
Spherical granulation requires very low airflows compared to top spray granulation. Final particle size is determined by spray rate, atomization pressure, and temperature; sphericity is determined by rotor speed.

Granules processed in a conical rotor exhibit a number of favorable characteristics including superior flowability and compressibility from its spherical shape. Fine control of the conical rotor process results in very narrow particle size distributions. Minimal excipients are used, so each granule contains up to 97% active content. Granule-to-granule content uniformity is superior to other granulation methods.

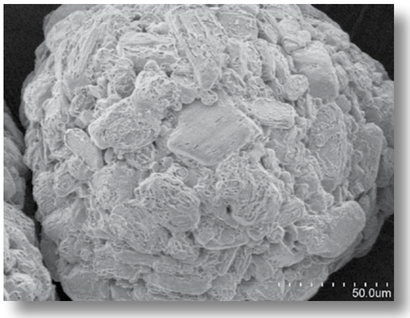
The goal of the study was to produce 90% active spherical granules with a particle-size distribution between 200-250 microns, starting with micronized ibuprofen with an average particle size of 20 microns. Using a 350mm conical rotor insert, a dry blend consisting of micronized ibuprofen and PVP K30, and a binder solution of deionized water and PVP K30 was processed.

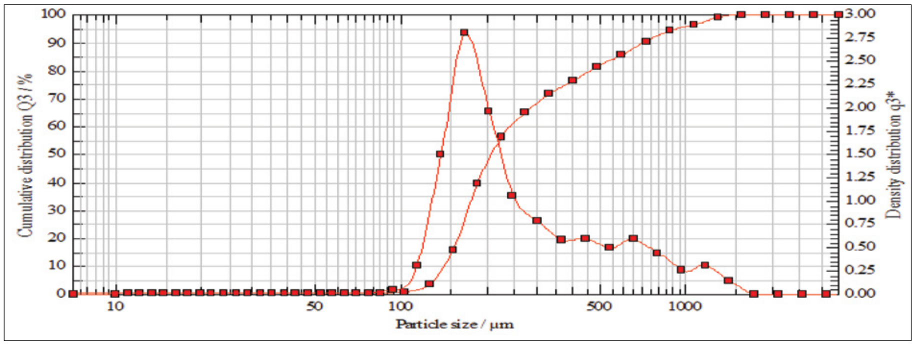
Equipment	
FC-LAB 3 with GXR-35 Rotor Insert	
Dry Blend	**Amount**
Micronized Ibuprofen	1.950 kg
PVP K-30	0.050 kg
Binding Solution	**Percent**
Deionized Water	90
PVP K-30	10
Process Parameters	**Set Point**
Slit Airflow	10 CFM
Slit Air Temperature	50° C
Rotor Speed	350 rpm
Spray Rate	16 g/min
Nozzle Air Pressure	2 bar
Total Process Time, Includes Drying	43 min
Atomization Pressure	2 bar

Starting Material



Final Product





Above: Particle size distribution via QicPic image analysis

Results:

The process produced very small, uniform granules, with a mean particle size of 212µ. Process yield was over 97%, total process time (including drying) was only 43 minutes, and the final beads contained 93% ibuprofen.

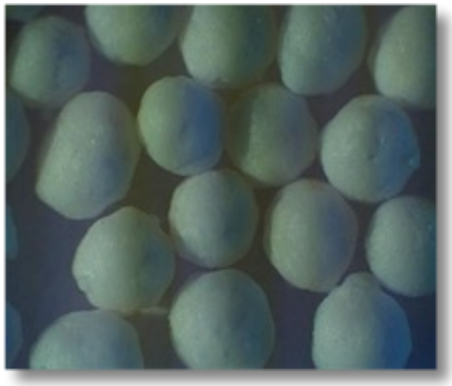
Method 2: Powder Layering, Active Pharmaceutical Ingredient

In the powder layering process, micronized API powder is dispersed via a precision powder feeder onto a core material, which is usually a sugar/starch, MCC or salt sphere, but is not limited to those materials. A binder solution binds the active powder to the outer surface of the core material, and by using proper balance between the powder feed rate and binder spray rate, precise coating levels and particle sizes can be achieved in a much shorter time than alternate coating methods.

Applying the active powder in dry form not only significantly reduces process time, it also eliminates the need to dissolve or suspend the active material in a liquid, which eliminates solution preparation time and in many cases reduces or eliminates the need for organic solvents. Layered beads with multiple actives can also be produced via powder layering, allowing for unique dosing and delivery of the active. Again, very narrow particle size distributions are achieved.

In the study, the goal was to achieve a uniform, smooth 75% loading of Flurbiprofen onto 30/35 mesh sugar sphere using a 5% PVP K30 binder solution. Following the drug layering, a coating of Eudragit RS-30D was applied to achieve a sustained release dosage.

Equipment	
FC-LAB 3 with GXR-35 Rotor Insert	
Cores	**Amount**
35/40 Mesh (420-500u) NP (Sugar Starch)	500 g
Powder Feed	
Micronized Flurbiprofen	2000 g
Binder Solution	
Deionized Water	304 g
PVP K-30	16 g
Process Parameters	**Set Point**
Airflow	10 CFM
Spray Rate	6-15 g/min
Powder Feed Rate	12-40 g/min
Rotor Speed	200 rpm
Inlet Temperature	50°C
Product/Exhaust Temperature	17°C/19°C
Total Process Time	65 min



Finished Product
Shape: Spherical, Smooth
Size: 100% between 600-650μ
Density: 0.69 g/cc
Flowability: Very Good

Results:

The process resulted in a very uniform coating with 99.1% usable yield finished material. The finished beads contained 75% API loading and no organic solvents were required. The process was completed in only 65 minutes, when an identical weight gain in a Wurster coater would have taken upwards of 300 minutes and would have required the use of organic solvents along with several solution preparation steps.

Method 3: Powder Layering

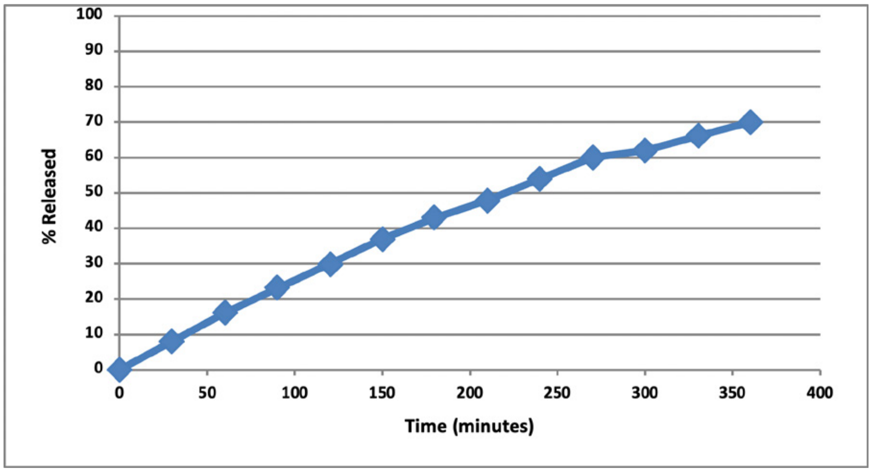
In addition to applying an API to a core, the conical rotor can also be used to apply a polymer powder to an active core to achieve desired release profiles. When coating with polymers, a plasticizer solution is used to bind and plasticize the polymer rather than a standard binder solution. Again, by attaining the critical balance between powder feed rate and binder spray rate, precise coating levels and particle sizes can be achieved in a shorter time than with alternate coating methods.

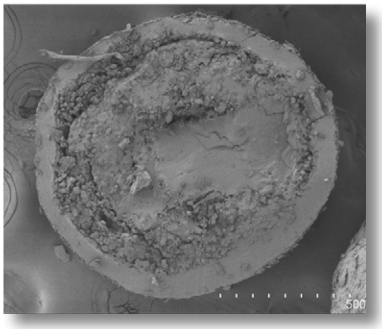
As with API layering, significant process time savings can be accomplished by applying the polymer as a dry powder rather than applying via solution or suspension, so use of organic solvents can be reduced or eliminated and very narrow particle size distributions are achieved with no agglomeration. Process yields up to 99% and superior coating uniformity are possible with the polymer powder layering process.

20-25 mesh sugar/starch beads were coated to a 60 mg/g active content with acetaminophen to act as a marker drug for dissolution testing. Dry polymer was layered onto the beads using a 350mm rotor insert and a K-Tron precision powder feeder. The active beads were coated with Ethocel Premium 10 FP (Dow Chemical), a sustained release polymer, HPMC-AS (Shin-Etsu), an enteric polymer and Eudragit E-PO (Evonik-Degussa), a taste masking polymer. The polymers were adhered to the beads and plasticized using a suspension of tri-ethyl citrate (TEC) or dibutyl sebacate (DBS) emulsified in water using Tween 80. The beads were coated to a 30% w/w polymer content. Dissolution and taste masking testing was done to verify that proper performance of the polymers.

Equipment	
FC-LAB 3 with GXR-35 Rotor Insert	
Beads	**Amount**
Acetaminophen Beads	2000 g
Dry Polymer	
Ethocel Premium 10 FP	857 g
Plasticizing Suspension	
Triethyl Citrate (TEC)	290 g
Tween 80	2 g
Deionized Water	683 g
Process Parameters	**Set Point**
Airflow	10 CFM
Powder Feed Rate	10 g/min
Spray Rate	10 g/min
Product Temperature	18°C
Total Process Time	100 min

Dissolution Chart





Mean Particle Size, X50: 862μ
Film Thickness: 50μ
Density: 0.652 g/cc
Coating Percentage: 30%
Active Loading: 61 mg/g
Yield: 96.1%

Results: Sustained Release Polymer

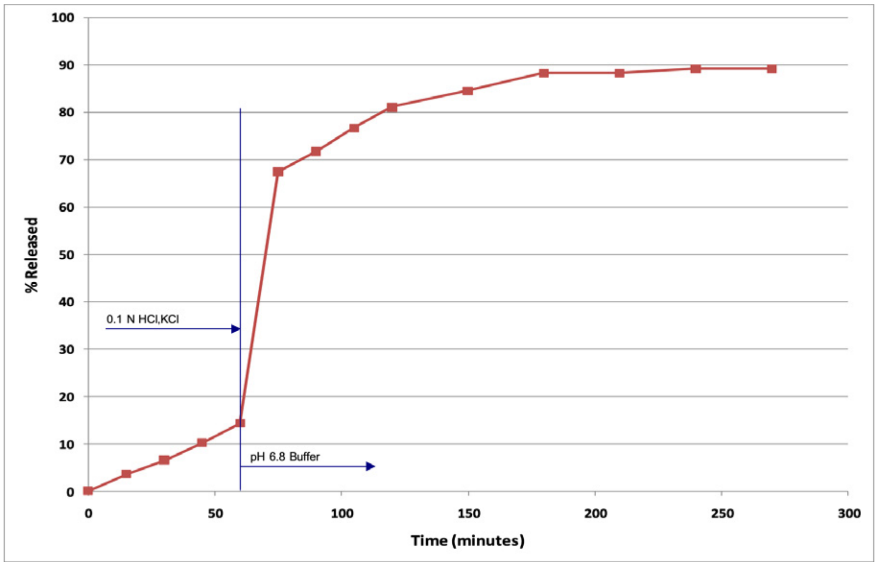
The finished beads were uniform and very smooth in appearance. The addition of the plasticizer throughout the powder layering process aided with formation of a uniform film on each bead. By eliminating the need to dissolve the polymers in a solvent and spray them onto the beads, significant time savings was achieved compared to conventional methods.

Precise airflow control allowed the finely divided polymer to remain in the product bed and produced extremely high application efficiency. Dissolution testing showed that the release of the active was delayed as expected.

Method 3: Powder Layering

Results: Enteric Release Polymer

The finished beads were extremely uniform and smooth, with a coating of 30% being reached in only 85 minutes. The final yield for the trial was 97.2%. Dissolution testing showed enteric protection was achieved, although there was slight leakage during the 60 minute acidic phase. Further process optimization could reduce the acidic leakage even further.



Equipment	
FC-LAB 3 with GXR-35 Rotor Insert	
Beads	**Amount**
Acetaminophen Beads	2000 g
Dry Polymer	
HPMC-AS 5.5	857 g
Plasticizing Suspension	
Triethyl Citrate (TEC)	330g
Tween 80	2 g
Deionized Water	683 g
Process Parameters	**Set Point**
Airflow	17 m3/hr
Powder Feed Rate	10 g/min
Rotor Speed	300 rpm
Product Temperature	18°C
Total Process Time	85 min

Equipment	
FC-LAB 3 with GXR-35 Rotor Insert	
Beads	**Amount**
Acetaminophen Beads	1000 g
Dry Polymer	
Eudragit E PO	400 g
Plasticizing Suspension	
Dibutyl Sebacate (DBS)	33 g
Tween 80	1 g
Deionized Water	330 g
Process Parameters	**Set Point**
Airflow	10 CFM
Powder Feed Rate	10.0 g/min
Spray Rate	8.0 g/min
Product Temperature	18°C
Total Process Time	40 min

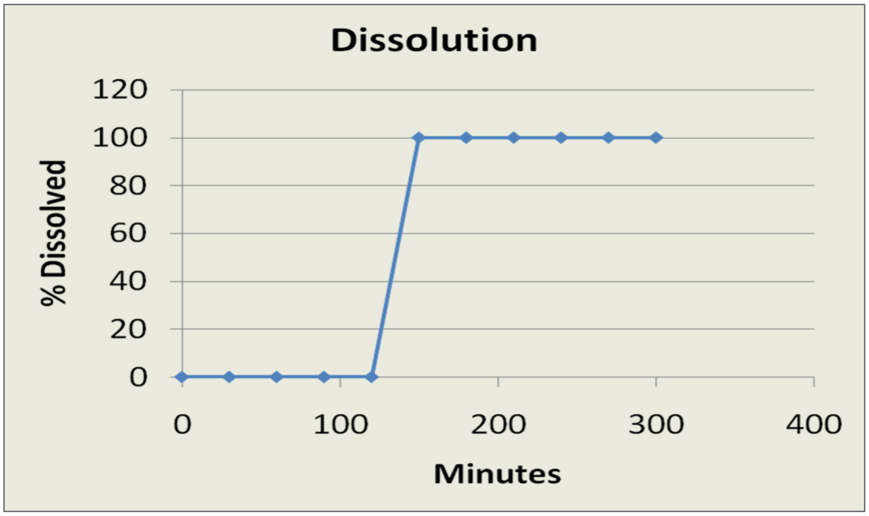
Results: Taste Masking Polymer

Taste masking was determined by having a panel of 7 volunteers place 300 mg of the coated pellets on the tongue for 60 seconds. It was determined that complete taste masking was accomplished at coating weight gains of 5% and higher. Dissolution showed that 100% of the drug was released within 5 minutes of testing in the pH 1.2 media, which would be expected for the E PO polymer system.

Method 4: Solution/Suspension Spray Coating

With spray coating in a rotor, an API or polymer is dissolved or suspended into a liquid to be sprayed onto a multi-particulate core, similar to the Wurster coating process. However, glidants can be added as dry powders, removing them from the solution, resulting in increased spray rates and reduced spray gun and solution line plugging, as well as reducing the required amount of glidant. Coating with the conical rotor processor resulted in very high coating uniformity and yields with excellent film quality and dissolution results. Unlike spherical granulation and powder layering, the solution/suspension coating process requires higher airflow during the process, which is introduced via a duct from the top of the unit.

A comparison was done between the conical rotor coating process and the Wurster process to apply a 10% enteric coating onto a 2 kg batch of APAP beads. The glidant (talc) was applied in dry form via a K-Tron precision powder feeder. With no glidant in the suspension, spray rates much higher than those possible in a Wurster processor were achieved.

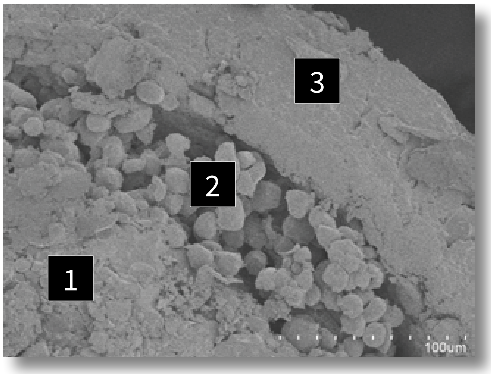


Equipment	
FC-LAB 3 with GXR-35 Rotor Insert	
Materials	**Amount**
APAP Coated Beads	2 kg
Coating Solution	
Polymer (Eudragit L-100)	0.666 kg
Acetone	5.333 kg
Triethyl Citrate (TEC)	0.066 kg
Glidant	
Talc	0.195 kg
Process Parameters	**Set Point**
Airflow (Slit/Fluid)	20/70 CFM
Slit Air Temperature	60°C
Product Temperature	34°C
Rotor Speed	300 rpm
Spray Rate	78 g/min
Total Process Time, Including Drying	95 min

Results:

With conical rotor coating, the coating surface is very smooth and dissolution profiles were as desired. The yield for this process was over 97%.

The amount of glidant required for the process was reduced by almost 50% by applying it in dry form versus suspending it in the coating solution. By eliminating the glidant in the solution, spray rates were increased by 50% over that of a comparatively-sized Wurster processor and solution line build-up and gun plugging were eliminated, which greatly reduced process and cleaning times.



1) Core, 2) API Layer, 3) Enteric Coating

Longstanding Trusted Source, Constant Innovation

The technological know-how developed by FREUND has resulted in a diverse range of products and services.

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