DISCUSSION OF PROCESSES WHICH UTILIZE CONICAL ROTOR TECHNOLOGY (SPHERONIZATION OR SPHERICAL GRANULATION, POWDER LAYERING OF ACTIVES OR POLYMERS, CONVENTIONAL SOLUTION/SUSPENSION APPLICATION OF ACTIVES OR POLYMERS)

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PURPOSE

To develop and introduce several novel processing methods which can be done with conical rotor technology. These methods include spherical granulation, powder layering, and solution/suspension coating.

METHODS: 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.

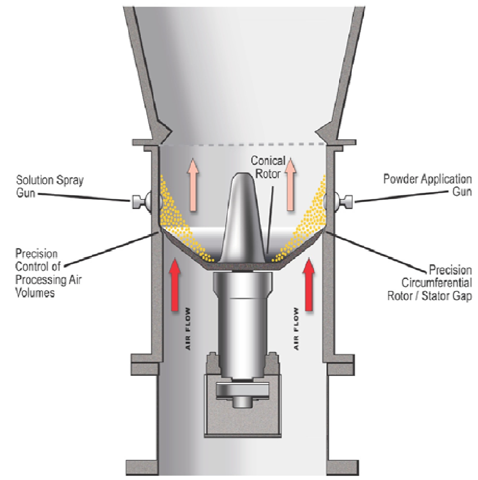
Granules processed in a conical rotor exhibit a number of favorable characteristics including superior flowability and compressibility from its spherical shape. Fine control of the conical rotor process results in very narrow particle size distributions. Minimal excipients are used, so each granule contains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

The goal of the Vector 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.

PROCESS: SPHERICAL GRANULATION

DRY BLEND	Amount
Micronized Ibuprofen	1.950 kg
PVP K30	0.050 kg
BINDING SOLUTION	**Percent**
Deionized Water	0.90
PVP K30	0.10
PROCESS PARAMETERS	**Setpoint**
Slit Airflow	17 m^3/hr
Slit Air Temperature	50°C
Rotor Speed	350 rpm
Spray Rate	16 g/min
Nozzle Air Pressure	2 bar
Total Process Time, including Drying	43 min
Atomization Pressure	2 bar

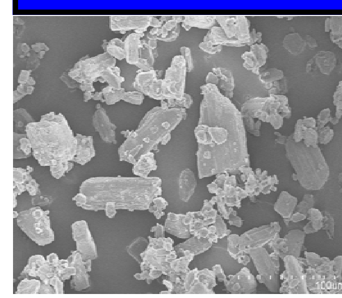
CONICAL ROTOR EQUIPMENT



CUTAWAY VIEW OF GXR ROTOR

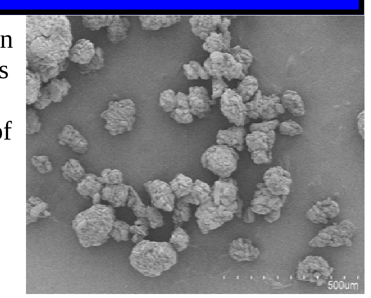
VFC-LAB 3 WITH GXR-35 INSERT

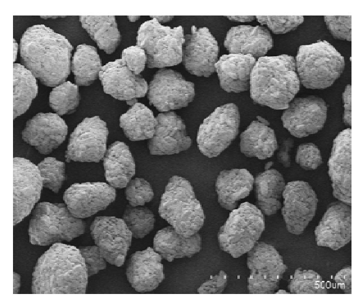
RESULTS: SPHERICAL GRANULATION



Left: Crystalline Ibuprofen before granulation process

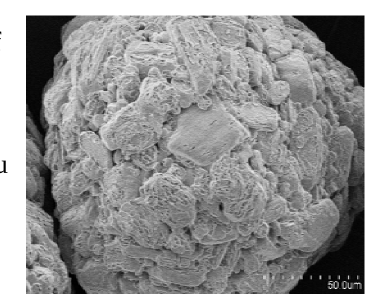
Right: After 10 minutes of processing





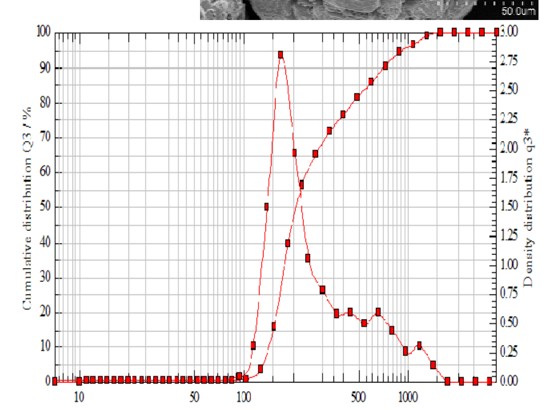
Left: After 30 minutes of processing

Right: Ibuprofen granule after processing, size 250µ



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

Finished Product
Shape: Spherical
Size: 212 microns
Density: 0.59 g/cc
Flowability: Very Good



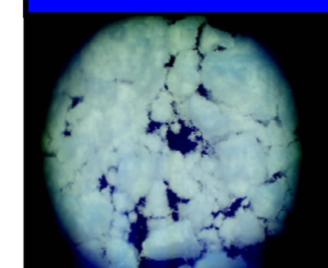
METHODS: POWDER LAYERING, ACTIVES

In the powder layering process, micronized API is dispersed via a precision powder feeder into a core material, which is usually a sugar/starch or salt sphere. Binder solution binds the active powder to the outer surface of the core material, and by using proper balance between powder feed rate and binder spray rate, precise coating levels and particle sizes can be achieved in a shorter time than alternate coating methods.

Significant process time savings can be accomplished by adding API in powder form rather than applying via solution/suspension, so use of organic solvents can be reduced or eliminated. Layered beads with multiple actives can be produced via powder layering. Again, very narrow particle size distributions are achieved.

In the Vector study, the goal was to achieve a uniform, smooth 30% powder layer of API (acetaminophen) onto a 30/35 mesh sugar sphere with 5% PVP K30 binder solution. Using the 350mm conical rotor insert and a K-Tron KT20 powder feeder, a 5% PVP K30 solution was used to bind the micronized APAP to the sugar spheres.

PROCESS: POWDER LAYERING, ACTIVES



Starting Material Characteristics of APAP:

- Needle-shaped API
- Size: 95% < 26µ
- API Density: 0.24 g/cc
- Flow Properties: Very Poor

CORES	Amount
45/50 Mesh (300-350µ) Sugar Starch NP	2000 g
POWDER FEED	
Micronized Acetaminophen	1000 g
Fumed Silica	10 g
BINDER SOLUTION	
PVP K30	16 g
Deionized Water	304 g
PROCESS PARAMETERS	**Setpoint/Change**
Airflow	17 m^3/hr / increased to 25 m^3/hr
Spray Rate	6.0 g/min / increased to 9.5 g/min
Powder Feed Rate	12.0 g/min / increased to 19.0 g/min
Rotor Speed	300 rpm / increased to 350 rpm
Inlet Temperature	50°C
Product/Exhaust Temperature	17°C / 19°C
Total Process Time	55 min

RESULTS: POWDER LAYERING, ACTIVES

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

The process resulted in a very uniform coating with 99.1% usable finished material. No organic solvents were required. The process was completed in only 55 minutes, using a drug addition rate of 18 g/min, compared to the 180 g/min spray rate required to achieve the same process time when coating with a solution.

METHODS: POWDER LAYERING, POLYMERS

In addition to applying an API to an inactive 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 suspension, so use of organic solvents can be reduced or eliminated and very narrow particle size distributions are achieved. Process yields up to 99% and superior coating uniformity are possible with the polymer powder layering process.

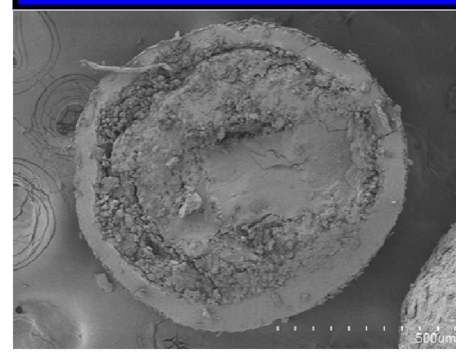
In the Vector study, 20-25 mesh sugar/starch beads were coated to a 60 mg/g active content with acetaminophen to act as a marker drug for dissolution testing. Dry polymer was layered onto the beads using a 350mm rotor insert and a K-Tron KT20 powder feeder. The active beads were coated with Ethocel Premium 10 FP (Dow Chemical), a sustained release polymer. The polymers were adhered to the beads and plasticized using a suspension of triethyl citrate (TEC) emulsified in water using Tween 80. The beads were coated to a 30% w/w polymer content. Dissolution testing was done to verify that proper release profiles were achieved.

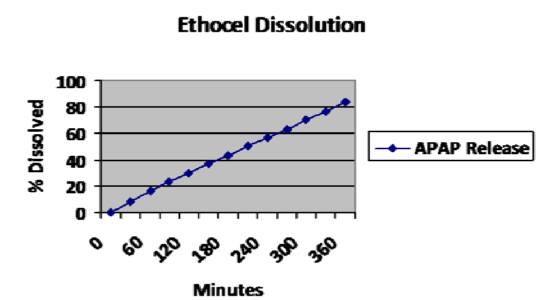
PROCESS: POWDER LAYERING, POLYMERS

BEADS	Amount
Acetaminophen Beads	2000 g
POLYMER	
Ethocel Premium 10 FP	857 g
SUSPENSION	
Triethyl Citrate (TEC)	290g
Tween 80	2 g
Deionized Water	683 g

PROCESS PARAMETERS	Setpoint
Airflow	17 m^3/hr
Powder Feed Rate	8.0 g/min
Rotor Speed	300 rpm
Product Temperature	18°C
Total Process Time	100 min

RESULTS: POWDER LAYERING, POLYMERS





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.

FINAL CHARACTERISTICS	
Mean Particle Size, X_{50}	862 µ
Film Thickness	50 µ
Density	0.652 g/cc
Coating Percentage	30.0%
Active Loading	61 mg/g
Yield	96.1%

METHODS: SOLUTION/SUSPENSION COATING

With spray coating in a rotor, an API or polymer is dissolved or suspended into a liquid to be sprayed onto a multiparticulate 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 results 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 airflows for drying.

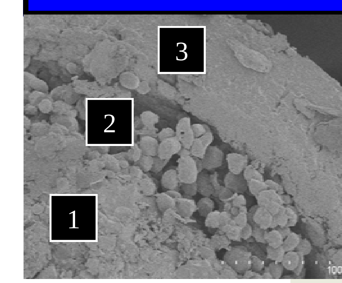
In the Vector study, a comparison was done between the conical rotor coating process and the Wurster process to apply a 10% enteric coating onto a 2 kg batch of APAP beads. The glidant (talc) was applied in dry form via a K-Tron KT20 powder feeder. With no glidant in the suspension, spray rates much higher than those possible in a Wurster processor were achieved.

PROCESS: SOLUTION/SUSPENSION COATING

MATERIALS	Amount
APAP Coated Beads	2.0 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	Setpoint
Slit Airflow (Coating/Drying)	60/160 m^3/hr
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

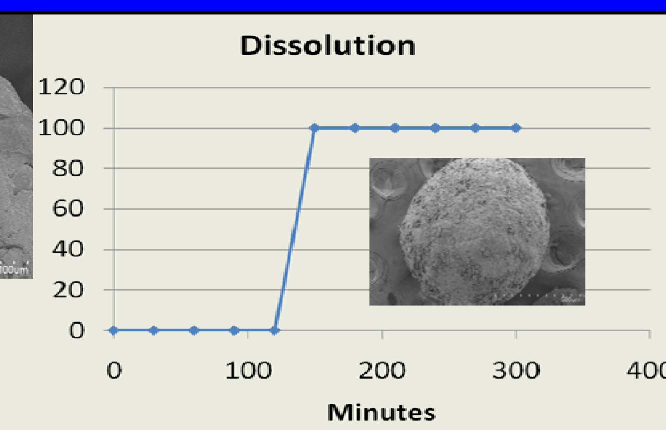
RESULTS: SOLUTION/SUSPENSION COATING



1. Core

2. API Layer

3. Enteric Coating



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.

CONCLUSIONS

Vector'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 decreased process times and reduced material (organic solvents, glidants, etc.) requirements resulting in lower costs and higher active content. Other advantages to the conical rotor system are higher yields than other granulators and coaters; the ability to finely control process parameters and product movement for high uniformity, flowability, and density; the ability to introduce multiple actives in the same bead; and "one-pot processing" to further reduce process and product handling times.