

Background: Tablet Operations

The compressed tablet is one of the most widely prescribed oral solid dosage forms in use today. Typically the ingredients which comprise the tablet blend include the active pharmaceutical ingredient (API) together with various excipients which not only act as carriers for the drug compound, but which also enhance its therapeutic effect, or efficacy. In order for the tablet press to produce quality tablets, it is imperative that the blend of ingredients sent to the press be dry and of uniform particle size. In addition, it is important that the API be evenly distributed within each tablet that is produced. If this cannot be done simply through adequate blending, the ingredients must go through an additional granulation step prior to the compression step of the press in order to ensure an even distribution of the API in the final tablet.

Three different techniques can be utilized for preparation of the mix prior to the compression stage: direct compression, dry granulation, or wet granulation. Direct compression is ideal for powders which can be mixed well and do not require further granulation steps prior to introduction to the tablet press. Dry granulation refers to the process steps of blending the ingredients followed by compaction and size reduction of the mix in order to produce a granular, free flowing blend of uniform size. Finally, wet granulation involves the production of a granule by the addition of liquid binders to the powder mixture.

Both continuous direct compression (CDC) and continuous mixing for the dry granulation processes involve the individual loading and accurate feeding of the API and a variety of excipients to a continuous blender. In addition, a separate feed device is used to continuously feed a lubricant (e.g. magnesium stearate) to the blender. Lubricants



Coperion K-Tron P-Series refill receiver above Coperion K-Tron LIW feeder

are added to the mix to improve powder flow so that the die of the tablet press fills accurately. (For further information on lubricant feeding direct to the tablet press, see Coperion K-Tron application sheet „Tablet Press Lubrication“)

The proper proportioning of pharmaceutical ingredients is

critical to the overall blended product quality and subsequent efficacy of the drug compound. Therefore, the accuracies of the feed and subsequent continuous refill technologies are critical. Typically, Coperion K-Tron Twin Screw Pharmaceutical Design Loss-in-Weight (LIW) feeders in conjunction

with Coperion K-Tron P-Series vacuum receivers are used for this purpose.

Continuous Processing

The emergence of the continuous philosophy used in the blending operations of either direct compression or dry granulation offers several key technical and process advantages. These advantages include the following:

- Smaller equipment size and layouts for longer periods of time
- Smaller space and utility costs: ideal situation for grass roots facilities
- Labor cost reduction due to automation and less manual requirements
- Reduction in overall operating costs
- Production of tighter specifications products, with higher and more consistent product quality

It should be noted that all of the above advantages improve overall profitability, a goal of significant importance to the pharmaceutical industry.

LIW Feeders and Continuous Blending

Typical residence times in the continuous mixers are minimal, often a matter of a few seconds. The rate of feeding and accuracy of delivery of product is critical to the overall blend uniformity. In many cases, the blender actually becomes a slave to the feeders, with the feeder mass flow rate being the key variable in the resultant end product. In most cases, several feeders are used at the inlet to the blender, one for each excipient in the formulation, and one for the actual API. Since most pharmaceutical materials are poorly flowing materials, special care must be taken in

Continuous Pharmaceutical Dry Granulation and Direct Compression Tableting Processes

the design and execution of the feeder hopper, screw and agitator configurations in order to ensure a consistent flow of the components to the process.

LIW Principle

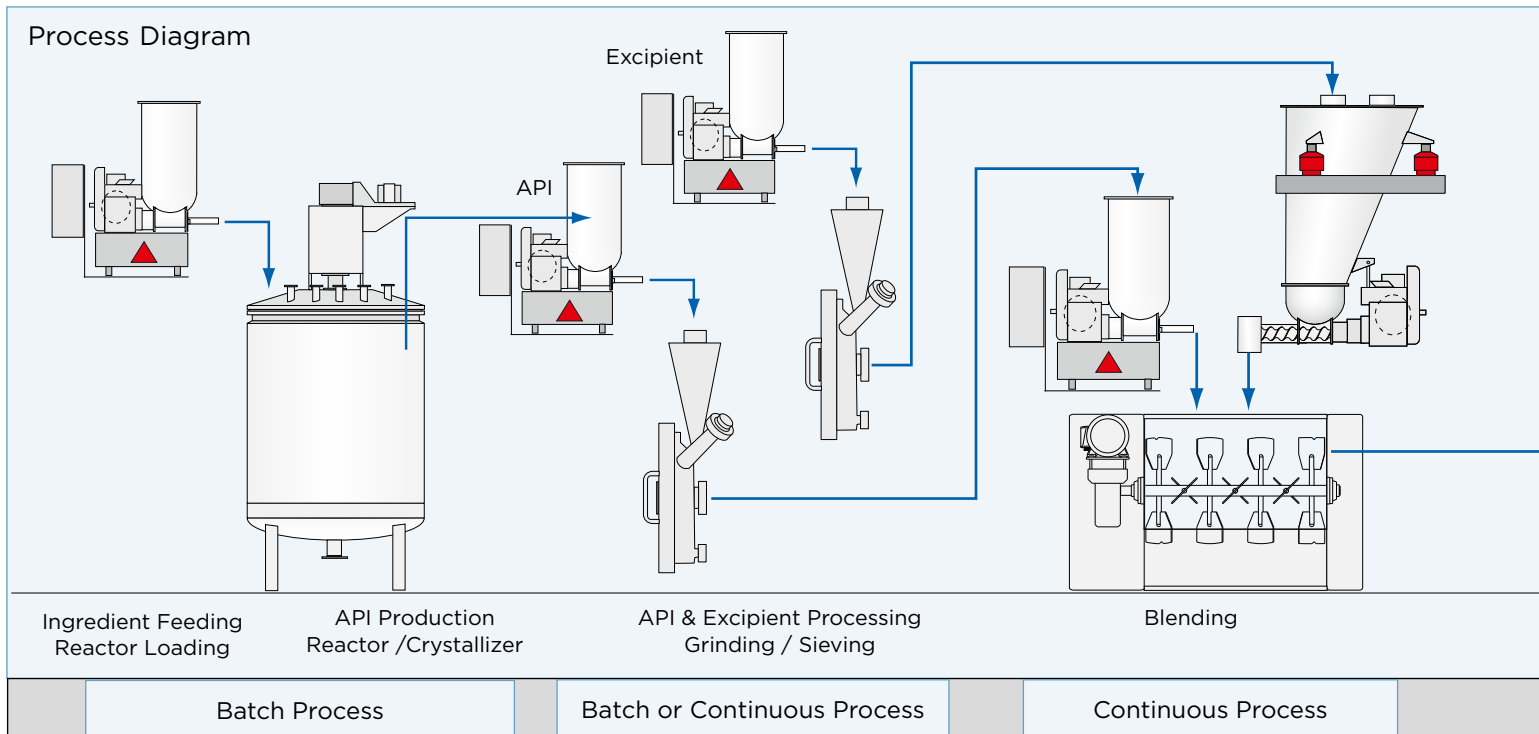
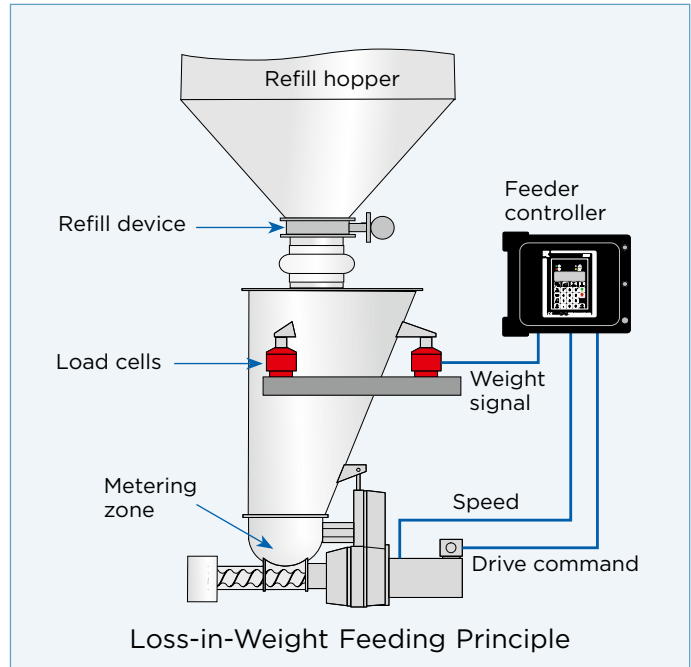
Coperion K-Tron pharmaceutical screw feeders can be supplied in either volumetric or gravimetric designs. However, due to the high accuracy requirements of feeding of continuous pharmaceutical processes, the gravimetric feeding principle via loss-in-weight feeding is mandatory. For example, when feeding materials with high variations in bulk density, volumetric feeders can have relatively high fluctuations in feed rate due to fluctuations in the filling of the screws. This fluctuation in feed rate results in inconsistencies in material delivery to the extruder below, thus resulting in variations in end product quality. In the case of cohesive materials, often the case with many API's and micronized excipients, it is

possible in volumetric mode to have relatively no material discharging while the screws are running, due to bridge building or packing in the hopper. Since the feed rate in a volumetric feeder is purely a function of screw speed, the feeder, and the mixing process below, have no way of detecting this error. Often even the use of level sensors in the feed hopper may not alert the process of this upset in a timely fashion, and off-spec product may result for a period of time.

Coperion K-Tron's gravimetric feeders utilize load cells with patented SFT technology to constantly measure the weight of pharmaceutical product delivered to the process below. Loss-in-weight feeding affords broad material handling capability and thus excels in feeding a wide range of materials from low to high rates. In operation, the entire feeder, hopper, and material are continuously weighed, and the feeder's discharge rate (which is the rate at which the feeding system

is losing weight) is precisely controlled to match the desired feed rate. With this technology, a constant mass flow is ensured, thus also ensuring for consistent

product output from the mixer/blender.



LIW Features

Coperion K-Tron gravimetric loss-in-weight twin screw feeders offer the following:

- Constant feed rate with high short term accuracy and low set point deviation
- Coperion K-Tron's patented SFT digital weighing technology delivers the high accuracy requirements needed for maintaining control of pharmaceutical systems
- Advanced SFT weighing technology features a resolution of 1:4,000,000 in 80 ms, as well as built in immunity to fluctuations in plant vibration and temperatures
- Simple measurement and validation of feed rate, via mass flow
- Gravimetric control consistently checks the hopper weight, thus alerting to any problems in flow to/from the feeder hopper
- Continuous level control by analyzing net weight

Material Delivery

The individual components of the pharmaceutical formulation can be delivered to the feeders in the form of either drums, flexible containers (FIBC's), or intermediate bulk containers (IBC'S). Typical design considerations which are incorporated into the overall material handling design include product/process containment, the method of cleaning/cleaning philosophy, and space limitations. The diagram on page 4 illustrates one such FIBC delivery method, with a special contained multi-liner product discharge, for the case of active ingredients. In the case of smaller volumes of the API, delivered at a much lower rate of feeding, a glove box or canister with a split butterfly valve for containment can be utilized.

LIW Refill

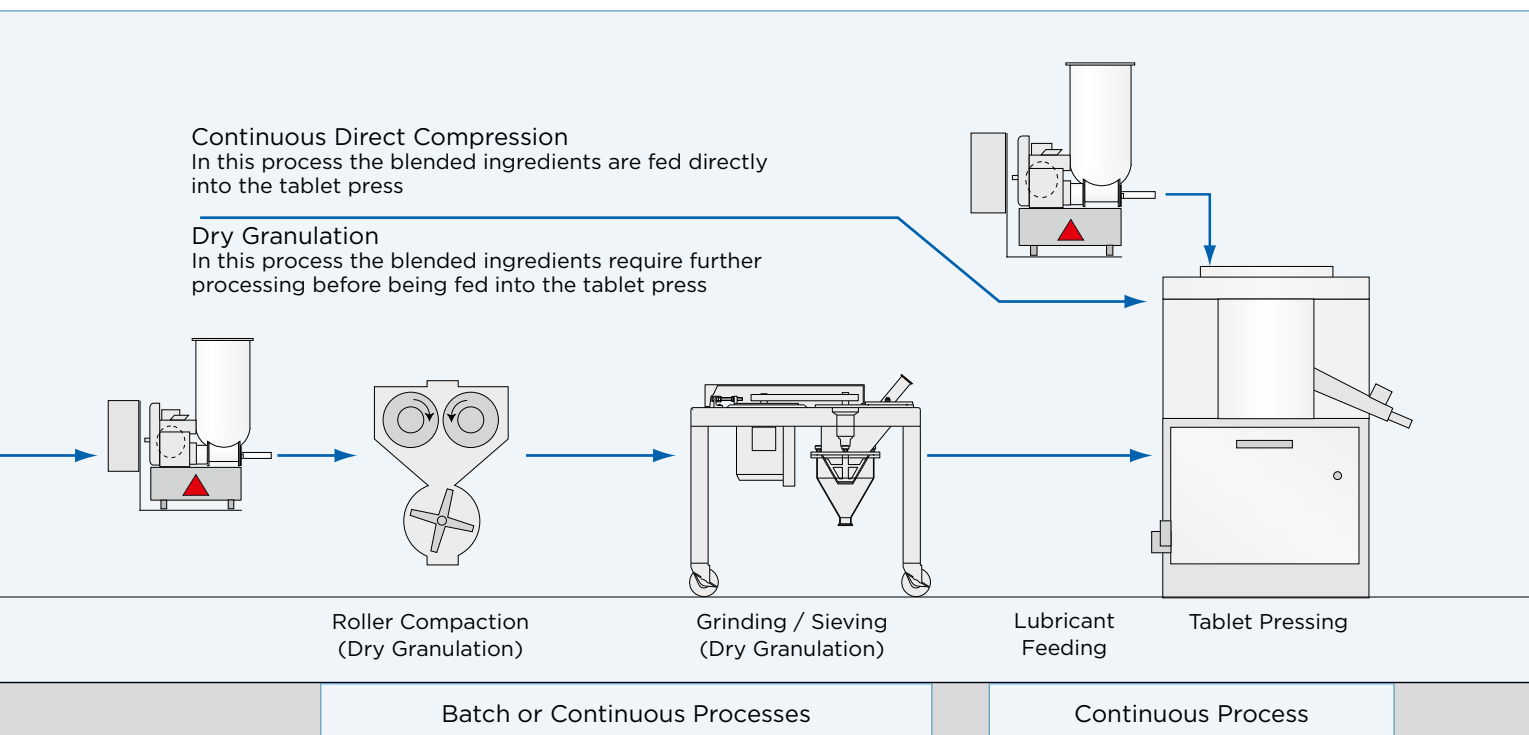
The mode of refill of product to a Loss-in-Weight (LIW) feeder that is feeding a continuous direct compression process can

be almost as critical as choosing the right feeder technology. Since the objective is to refill the feeder as quickly as possible, the use of pneumatic receivers that operate under a dilute phase vacuum transfer principle are often used as refill devices, particularly for continuous operations. The photo on page 1 shows a Coperion K-Tron P-Series receiver above a LIW feeder.

When refilling in a continuous pharmaceutical process it is imperative that the refill devices be reliable to maintain constant flow of either the API or excipient to the process, which is sufficient to avoid exceeding a specific refill time limit. This time limit must be relatively short, in order to allow the feeder to return to a true gravimetric operation, and ensure constant mass flow of the product to the process. Additionally, the flow cutoff action of the selected device must be quick and sure. A slow tapering off of the refill flow needlessly lengthens refill time. Any leakage of the refill

device may cause an unavoidable measurable weight disturbance, but will always result in a flow error in the positive direction.

There are several choices for the type of valves utilized. Options include knife gates, flap valves, modulating butterfly valves or rotary valves. Butterfly valves are usually the valve of choice in the pharmaceutical industry due to their easy clean design, and also due to their availability in high containment options. (NOTE: for further details on refill operations, see Coperion K-Tron application sheet "Refilling Loss-in-Weight Feeders via Pneumatic Conveying in Continuous Pharmaceutical Processes")



Continuous Pharmaceutical Dry Granulation and Direct Compression Tableting Processes



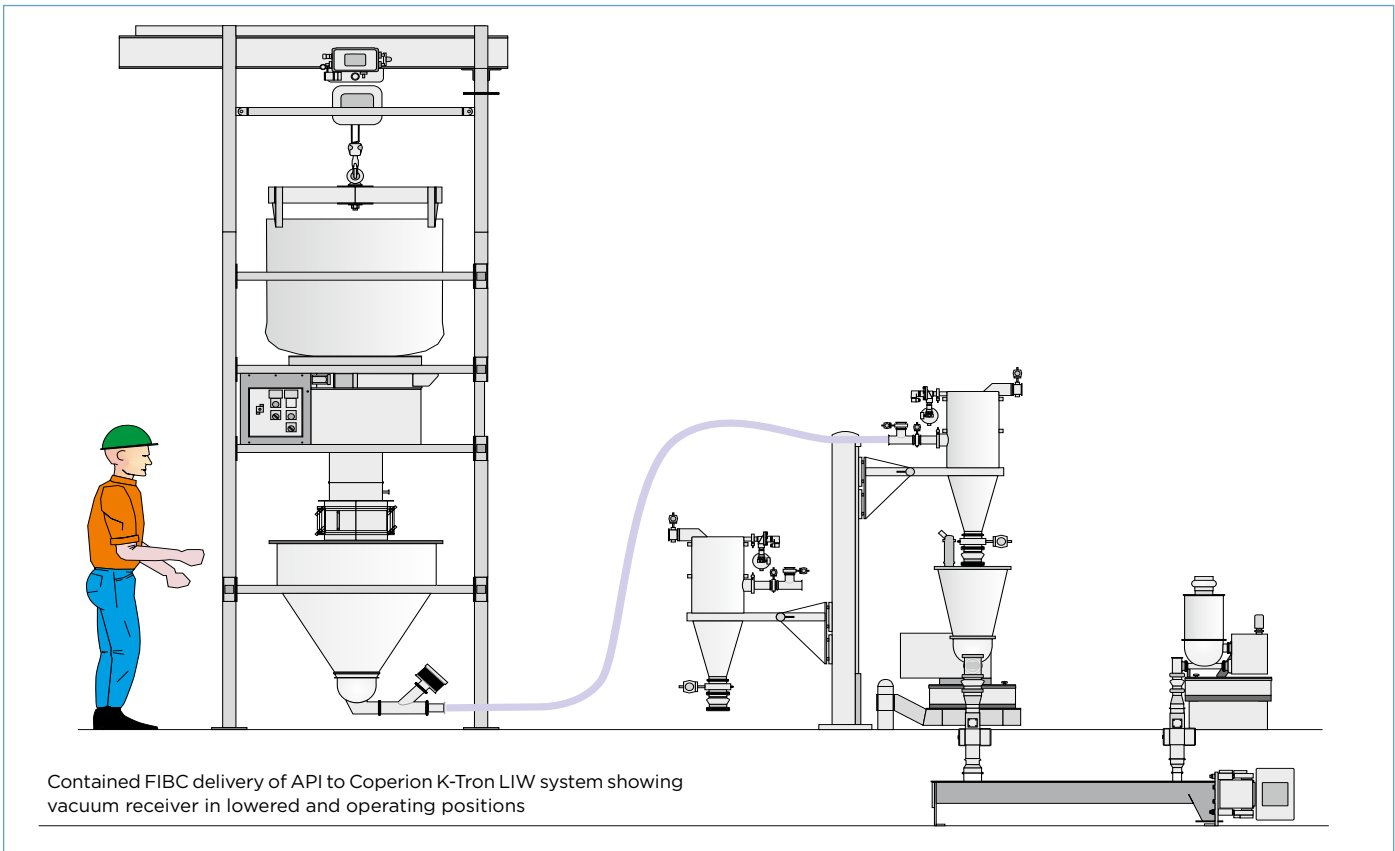
Coperion K-Tron Advantage

- The Coperion K-Tron Pharma feeder is designed specifically for the pharmaceutical industry, all cGMP constructed and designed, with ease of cleaning in mind
- Coperion K-Tron is able to provide a wide variety of screw and agitator designs, in order to give best results for a wide variety of ingredients
- The P-Series line of pneumatic receivers is designed for cleanability and ease of access, with all materials of

- construction FDA approved.
- Coperion K-Tron's patented SFT digital weighing technology delivers the high accuracy requirements needed for maintaining control of the addition of costly ingredients
- Refill Array as provided with Coperion K-Tron controller also allows for consistent fill and quality
- All components include a quick clean, easy disassembly design complete with fully welded and polished housings and triclover clamps/ferrules
- All product contact parts are constructed to conform with strict cGMP standards and are standard in 316 stainless steel
- The Coperion K-Tron Systems Group can supply integrated systems of Coperion K-Tron and ancillary products, with one source management
- Coperion K-Tron can provide all controls and engineering including CFR 21 Part 11 based control platforms
- Coperion K-Tron can provide systems suitable for various containment and OEL levels, as well as specific cleaning and sanitation requirements



Coperion K-Tron pharma design twin screw loss-in-weight feeder



Manufacturing plants:

Coperion K-Tron Pitman, Inc.
 590 Woodbury-Glassboro Rd
 Sewell, NJ 08080, USA
 Tel +1 856 589 0500
 Fax +1 856 589 8113
 E-mail: info@coperionktron.com

Coperion K-Tron Salina, Inc.
 606 North Front St.
 Salina, KS 67401, USA
 Tel +1 785 825 1611
 Fax +1 785 825 8759
 E-mail: info@coperionktron.com

Coperion K-Tron (Switzerland) LLC
 Lenzhardweg 43/45
 CH-5702 Niederlenz
 Tel +41 62 885 71 71
 Fax +41 62 885 71 80
 E-mail: cks@coperionktron.com