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Continuous Powder Feeding for Pharmaceutical Solid Dosage Form Manufacture: A Short Review

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Abstract

There has been a noticeable shift from pharmaceutical batch processing towards a more continuous mode of manufacture for solid oral dosage forms. Continuous solid oral dose processes would not be possible in the absence of a highly accurate feeding system. The performance of feeders defines the content of formulations and is therefore a critical operation in continuous manufacturing of solid dosage forms. It was the purpose of this review to review the role of the initial powder feeding step in a continuous manufacturing process. Different feeding mechanisms are discussed with a particular emphasis on screw controlled (loss in weight) LIW feeding. The importance of understanding the physical properties of the raw materials and its impact the feeding process is reviewed. Prior knowledge of materials provides an initial indication of how the powders will behave through processing and facilitates in the selection of the most suitable (i) feeder (capacity) (ii) feeding mechanism and (iii) in the case of screw feeder - screw type. The studies identified in this review focus on the impact of material on powder feeding performance.

Keywords

Continuous manufacturing

Pharmaceutical powder properties

Loss-in-weight feeding

1 Introduction

In the last decade there has been a noticeable shift to move pharmaceutical manufacturing from a more traditional batch configuration to a continuous mode. Pharmaceutical regulatory authorities and manufacturers acknowledge the benefits of continuous manufacturing processing over the traditional batch configuration, in terms of cost-reduction, improved efficiency, ease of automation, better controlled processing, reduced energy, reduced waste, less footprint, ease of scale up, less material handling, and consistent product quality (1-3). Currently there are two approved commerical pharmaceutical products produced via continuous processes on the market. Vertex achieved FDA approval for a continuous process in the manufacture of the cystic fibrosis drug Orkambi, July 2015. In early 2016 the FDA approved, for the first time a change in production method from batch to continuous manufacturing for the production of the protease inhibitor Prezista (Darunavir) used in the treatment of HIV-1 infection (4).

The feeding of raw materials to downstream processes is a key process step in the continuous manufacture of any formulated product. Continuous powder processing requires a consistent, accurate and reliable feed stream of raw materials to produce quality products. Hence the initial feeding stage is critical to the entire manufacturing process. This is especially true in the manufacture of pharmaceutical solid dosage forms such as tablets, capsules and sachets. The ability to feed powder consistently and continuously is regarded as one of the critical requirements of the overall manufacturing process (5, 6). This becomes especially pertinent when feeding active pharmaceutical ingredients (API). If the feeder is incapable of dosing the powder feed at a desired rate it will pass any inconsistencies variability in composition and weight to downstream unit operations such as blending or granulation (7, 8). Inconsistent feeding can lead to quality failures such as out of specification dosage form assay and content uniformity.

Regulatory authorities, such as the FDA, are supportive of the move towards pharmaceutical continuous manufacturing (9). Successful continuous processing requires a high level of process control via in-process testing and improved process understanding to ensure that medicinal products are designed and produced with predictable and reproducible critical quality attributes. These process control requirements are in line with the development of the following frameworks: Quality by Design (QbD) (10) and Process Analytical Technology (PAT) (11). The primary objectives of the QbD and PAT frameworks are to work retrospectively, from the end user to initial product development, in order to ensure that the highest level of product quality is maintained throughout the product lifecycle (12). The QbD and PAT frameworks aim to facilitate the pharmaceutical community to attain a state whereby product quality and performance are accomplished and guaranteed by the design of effective, efficient and well understood manufacturing processes (10, 11). To fully understand a pharmaceutical manufacturing process it is necessary to understand the physicochemical properties of the raw ingredients involved, which are integral to the quality of the final product.

Interest in the area of continuous manufacturing has increased amongst industry and academics as is evident with the recent escalation of publications in this subject (3, 6, 8, 13, 14). It is apparent that review publications to date refer only to the blending or granulation steps of the continuous process train and that research articles examining the feeding process are limited (15, 16). This review examines the feeding step of the continuous manufacturing train with the intention to examine the criticality of raw material properties in relation to the feeding process. The review provides a brief overview of the principles and mechanism of continuous screw feeding, followed by a summary of studies which relate material properties to continuous feeding behaviour.

2 Powder Feeding

2.1 Loss in Weight (Gravimetric) Feeding

Loss in weight (LIW) or gravimetric feeding is the most commonly used continuous feeding method for pharmaceutical powders (12, 17). Despite different feeder set-ups being used for materials with varying physical properties, the general mode of operation and mechanisms are essentially equivalent. All LIW feeders generally consist of three parts (i) a volumetric feeder (ii) a weighing platform and (iii) a gravimetric controller, Figure 1.

The volumetric feeder is mounted on the top of the weighing platform which measures the mass of the feeder and the materials contained within. As material is dispensed via a feeding device, such as a screw, the controller acquires a signal from the load cell in the weighing platform as a function of time. As shown in equation 1, using the difference in weight (Δw_{feeder}) measured by the platform divided by the difference in time between successive measurments (Δt), the controller can determine the instantaneous feed rate ($-m_{feed}$)

$$\left(\frac{\Delta w_{feeder}}{\Delta t}\right) = -m_{feed} \qquad \textbf{Equation 1}$$

The actual weight loss (per unit time) is compared to a desired weight loss (per unit of time) based on a pre-programmed feed rate. Any discrepenacy between the actual and desired weight loss per unit of time results in a correction to the speed of the feeding device to maintain a steady feed rate, thus overcoming any variability in material bulk density (7, 18).

Gravimetric feeders can also operate in volumetric mode. In this instance bulk material is charged from a hopper with a constant volume per unit of time by regulating the speed of the feeding device (screws) and the volume of material dispensed is determined through calibration (18). In general, volumetric feeding is considered to be less reliable than gravimetric feeding due to the inherant nature of powders possessing variable densities due to prior processing, storage, environmental or processing conditions (17, 19). Volumetric feeders can be used in processes where the bulk density of the feed material is consistent or where feeder accuracy is less critical. As a result, the use of volumetric feeders is generally inappropriate for pharmaceutical continuous process applications that involve rigorous accuracy requirements, such as consistent API feeding. During a start up or a refill procedure LIW feeders revert to volumetric feeders momentarily resulting in a disruption to the process. This will be further discussed in section 4.

Whilst mechanically the feeder system is simple in principle, the behaviour of feed materials can be complicated. Such complications can arise due to variability in material characteristics such as flow properties, particle size and bulk density and differences in target feed rates. Issues such as bridging, rat holding, blockages, electrostatic formation can be observed during operation (18). LIW feeders have been developed in a wide range of sizes to overcome such challenges in feeding powders. In addition, replaceable tooling with various nozzle sizes, screw sizes and types have been developed to enable ingredients with large variations in material properties to be fed successfully (17).

2.2 Screw Feeders

The use of rotating screws is commonly used to dispense raw materials using LIW feeders. Screws can be selected to provide the optimum feeding conditions based on the characteristics of the materials being processed and the processing requirements such as pre-determined feed rate. For instance, screws are available in a single or double configuration, various thread depths and in spiral or auger configuration. LIW or volumetric feeders have individualised sets of tooling such as screws and screens that are only compatible with that feeder type (18, 20). Pre-determination of a desired feed rate based on material concentrations in the final dosage form and downstream process capabilities, such as tablet press or granulator throughput, is necessary in the selection of both a feeder and feeding configuration. Screw and screen selection based on material properties will be further discussed in section 4.

In addition to conventional LIW feeder designs discussed throughout this review, more novel micro-feeding approaches are reviewed by Besenhard et al. (2016) (21). The authors demonstrate a gravimetric powder feeding system with a vibratory sieve mounted on a chute which is capable of delivering a fair flowing powder that is sieved between 90 and 160 μm, at a feed rate of 0.1mg/s (RSD = 0.023) and 0.15 mg/s (RSD = 0.017).

3 Processing and material factors to be considered

Solid oral dosage forms are multi-component containing different ingredients such as diluents, lubricants, disintegrants, glidants and API(s). Each component will vary in particulate size and shape, bulk density, compressibility, flow, cohesive strength and moisture content, in addition to different concentrations in the final dosage form. Due to the multi-variate nature of raw materials, it is typically not straightforward to determine which properties will influence the feeding process most significantly. There is not one individual feeder design, configuration or size that can handle all the different material characteristics highlighted or the different throughput requirements of the process. For feeding to be successful, the key physical properties of the materials must be known and their behaviour during feeding fully understood.

The optimal feeding configuration or tooling selection is based on both the desired feed rate and powder properties. It is imperative to test and investigate each component separately to ascertain optimal feeding conditions. This involves determining the constraints in the feeder and feeding tooling for each individual component of the formulation, testing potentially successful configurations and comparing the feeding performance between the different configurations (22). Figure 2 illustrates an example of a guide to screw selection based on material characteristics (23).

It is recommended that single screws are used for free flowing powders which can easily fill the flights of the screws. Twin screw feeders are commonly used to transfer materials which are particularly free flowing but require additional control to regulate the flow. Twin screw feeders are also useful when the formulation contains cohesive materials where additional force is required to feed the material or to reduce adhesion to the screw threads. Free flowing materials tend to overfill the screw under the influence of gravity, whereas more cohesive materials may require increasing levels of agitation to facilitate flow into the screw (24). Some screw designs, such as concave screws are capable of 'self-cleaning' which is particularly useful when feeding cohesive powders which are difficult to handle, such as colloidal silicon dioxide or magnesium sterate (22). Auger screws have the advantage of having a higher capacity for powders which require higher throughput but do not have the self-cleaning function, and therefore would not be recommended for cohesive materials. There are a limited number of publications which directly discuss the impact of material properties on equipment selection and configuration. Table 1 details the continuous feeding conditions for a range of pharmaceutical materials with varying physical properties.

3.1.1 Influence of Powder Properties

A recent publication by Engisch and Muzzio (2015) demonstrated the influence of material properties on feeder and tooling selection (22). A range of feeders were tested with a range of pharmaceutical materials with varying physical charatersitics to highlight the challenges that can be encountered with feeding. For instance, in the case of freely flowing ProSolv HD90 at a feed rate of 13.3 kg/hr, a reduction in feeding performance was observed when tooling was selected which allowed the material to flow too freely. This resulted in the powder uncontrollably flushing through the flight of each screw with each rotation. The use of concave screws, which possess smaller flights and therefore smaller pulsations, resulted in increased control. Additional feeding control can be achieved with the inclusion of discharge screens. However, when testing a free flowing model API at a desired feed rate of 15.6 kg/hr, using concave screws, the presence of a discharge screen resulted in material clogging at the outlet, causing equipment to shut down. A more suitable feeder set-up for this powder was found by eliminating the discharge screen.

Cohesive, low density materials, such colloidal silicon dioxide and magnesium stearate are anticipated to be particularly problematic during continuous feeding. This is primarily due to material adhering to equipment surfaces. Engish and Muzzio (22) studied these materials with various tooling configurations to determine optimum conditions. The addition of optional tooling such as discharge screens resulted in build up of material at the outlet and therefore were eliminated. The use of concave screws were found to be most suitable as these possess a ‘self cleaning’ function. In the case of colloidal silicon dioxide it was determined that the material should not be fed individually but as a pre-blend with the API. This was due to the low density of the material and intense electrostatic properties causing it to adhere to the downspout on the feeder outlet. A static eliminator was used with this material reducing the RSD of the feed rate of the individual powder (at 0.4 kg/hr) from approximately 0.125% to 0.08%. As magnesium stearate is usually present in formulations in low amounts (< 2% w/w), microfeeders with lower throughputs, such as the KTRON MT12 or KT20 are typically more suitable.

Cartwright et al. (2013) compared a number of LIW feeders and configurations to feed a low density (0.14 g/ml), poor flowing API (26). Using the KTRON KT20 feeder, core and spiral screws were selected to feed this material with an adequate degree of control. It was reported that operator intervention was often required to prevent the formation of rat holes in the upstream hopper. A flexible frame feeder, the Brabender FW40 was able to deliver the API powder without manual intervention. Due to the low bulk density of the API (0.14 g/ml) a number of technical challenges were observed with flighted auger and fine concave screws. There was an increase in feeder motor torque over time due to the material under transport compacting within the screws as well as between the screws. This led to the feeder motor achieving maximum motor torque and shutting down as per safety controls. Fine concave screws were successful for excipient blends which were free flowing and of consistent density.

4 Sources of inconsistency in feeding

It takes a period of time following the initial start-up of a feeder for the equipment to reach a steady state of operation. It has been demonstrated that fluctuations in the mass flow of the powder compared to the pre-set feed rate are observed at the start of feeding. Once the mass flow is equal to the set point, the feeder is said to be at steady state. The time it takes to reach steady state is related to the time that it takes for powder to fill the flights of the screws before accurate feeding can begin. Simonaho et al. (2016) demonstrated this period to be 3 minutes following start up of the KTRON K20 feeding of microcrystalline cellulose at 17.1 kg/hr and acetylsalicylic acid at 2.9 kg/hr (6). Ervasti et al. (2015) reported that a 10 minute period was sufficient to reach equilibrium when feeding blend components at feed rates which ranged from 0.07 kg/hr to 2.24 kg/hr using two LIW feeders (K-ML-D5-KT20 and K-CL-SFS-KT20) (8). The study also illustrated that the relative standard deivation (RSD) from the feeder set point was highest at the lower API feed rates due to the independence of the absolute standard deviation of the feed rate. Data from the author's laboratory demonstrate that steady state (± 3σ) was attained at approximately 12 minutes for microcrystalline cellulose fed at 0.25 kg/hr using a KTRON MT12 LIW feeder, Figure 3.

Once steady state is achieved, random spikes in feed rates can occur and are commonly attributed to a range of factors; properties of the feed materials, equipment set-up (screw and screen selection), surrounding environmental vibrations and disturbances and during refill procedures when LIW feeders revert to volumetric feeders momentarily

Feeding cohesive materials introduces the risk of materials adhering to the screws and screens, forming lumps in the feeder and causing inconsistencies in the material flow. Accumulation of powder at the outlet of the feeder can result in the material dropping off causing a spike in the data read out. Some feeder models recommend the use of sieves at the screw outlet to prevent such accumulation of powder.

LIW systems may be exposed to physical disturbances such as oscillations, vibrations and air flow in the surrounding environment which can disturb the sensitive process of gravimetric feeding. Many feeders have mitigation in place in their design such as dampeners, homogenators and agitators. Feeder design can involve the use of vibration minimising flexible materials or stainless steel in their construction to aid the feeding (27, 28).

Powder processing operations such as screw feeding can generate vast quantities of electrostatic charge via the movement of powder through the equipment. Materials such as colloidal silcon dioxide possess intense electrostatic properties, causing the powder to displace a strong tendacy to adhere against material tooling or the outlet tube of a feeder. In order to reduce the effect of electrostatics, as mentioned previously, it can be necessary to equip the feeder with a static eliminater (22). Engisch and Muzzio have investigated this issue and were able to reduce, not eliminate, the impact of electrostatics on material build up (22).

As mentioned in section 2, disturbances during the hopper refill procedures are attributed to a decrease in feeding accuracy due to the changes from gravimetric to volumetric feeding.. During normal gravimetric mode of operation the feeder can respond to any changes in the density of the material and adjust the speed to maintain an accurate feed rate. During a refill procedure the equipment, in volumetric mode, is essentially rendered blind to any density changes of the incoming material. The density of the material can either (i) increase due to compression of the existing existing powder bed by the incoming material or (ii) decrease due to aeration of the powder due to the refill procedure (7). These changes in density are mainly due to the physical characteristics of the feed material. The level of disturbance during refill and the frequency of refill thereforecan be minimised by tailored hopper design to match the feed rate and specific material properties of the raw material being fed (7, 29). Engisch and Muzzio (2015) recommend that the quantity of refills should be based on reducing any deviation from the feed rate set point to a level that is acceptable to downstream unit operations (7). The importance of hopper fill level during a refill procedure was also clearly demonstrated in this study. Deviations from the set point were larger when the hopper was refilled at lower fill levels for example 20%. While, refilling the hopper at a 60% fill level results in more accurate feeding it also leads to a more demanding refill regime with more frequent, smaller refills.

5 Application of PAT in Continuous Feeding

At certain time points during the continuous manufacturing process, it will be necessary to examine the homogeneity of the powders streams. The in-line measurement of powder streams is challenging due to (i) frequent fouling of the measurement probe; (ii) difficulty in defining a 'sample size' and (iii) determination of the optimum probe position so it does not interfere with the powder stream and it only measures the powder stream and not powder adhering to the machinery (30). Additionally, the flow rate of a powder feed under a continuous process may be much faster than what is experienced during batch blender rotation, limiting the collection of reliable calibration data. (13).

There are limited studies discussing the application of PAT on continuous powder feeders where individual components are being dispensed. Typically, the most significant PAT application in this respect is identification of the feed component. However, there may be some applications where the feeding of blended material is required to ensure continuous movement of the blend through the process such as in roller compaction. When monitoring a blend, the primary goal of any PAT application is assessing API uniformity. In continuous manufacturing there is movement of blend from one unit operation to another which can introduce challenges in the interpretation of PAT spectra. A recent publication by Shi et al. (2015) focused on pretreatment methodologies to overcomethe impact of changing feed rate when assessing API potency in a blend spectroscopically (13). This work compared on-line NIR spectroscopic methods (Fourier Transform (FT) and dispersive spectrometers) to investigate blend uniformity of acetaminophen mixtures dispensed from a twin screw volumetric feeder (13). A PLS model was applied to spectral data collected at 0 kg/hr (static), 13.5 kg/h and 27.6 kg/hr. The pretreament of mean centering and SNV was used to reduce the RMSE of collected spectra thus reducing the variability due to changes in feed rate allowing to better monitor the changes in API. Singh and co-workers (2015) recently published a study using on-line NIR as a PAT tool to monitor bulk density of individual materials and blends at a feeder outlet. Interestingly this study demonstrated the impact of bulk density on the feeding mechanism and illustrated the link between variations in bulk density of feed materials and subsequent modification in feed screw speed to compensate for the changes (31).

6 Conclusions

The performance of powder feeders defines the content of the final dosage form and is therefore a critical unit operation in continuous processing of solid dosage forms. It was the aim of this review to highlight the importance of the initial powder feeding step in the overall manufacture of pharmaceutical solid dosage forms and focus on the impact of material properties on feeding performance and feeding equipment selection and set-up. The literature related to continuous feeding of pharmaceutical powders focuses primarily on the impact of powder properties on feeding parameter selection. However it is also important to consider the impact of feeding parameters on pharmaceutical powder properties during pharmaceutical processing and more research into this area is warranted.

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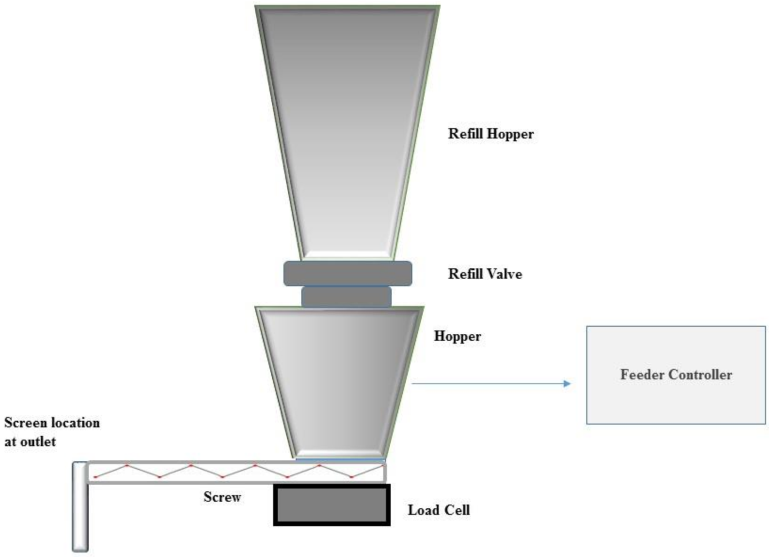
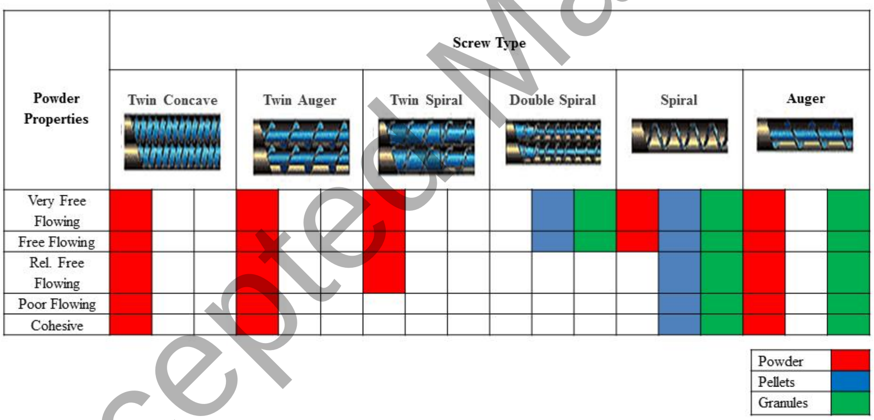
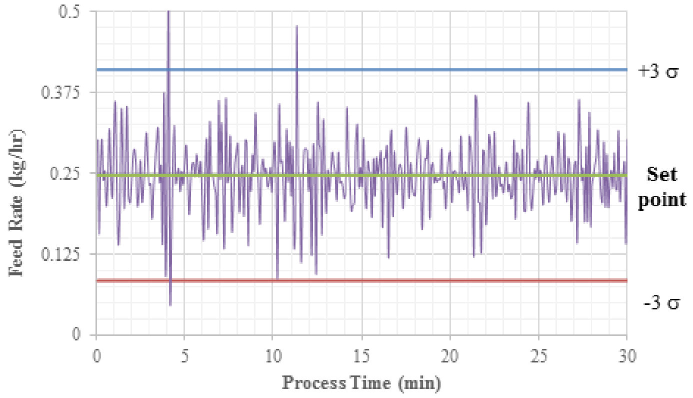

Refill Hopper
Refill Valve
Hopper
Feeder Controller
Screen location
at outlet
Screw
Load Cell


Powder Properties
Screw Type
Twin Concave
Twin Auger
Twin Spiral
Double Spiral
Spiral
Auger
Very Free Flowing
Free Flowing
Rel. Free Flowing
Poor Flowing
Cohesive
Powder
Pellets
Granules



0.5
0.375
0.25
0.125
0
Feed Rate (kg/hr)
0
5
10
15
20
25
30
Process Time (min)
+3 σ
Set point
-3 σ

Material	Function	Physical Properties Reported	Feed Rate (kg/h)	Feeder Model	Screw Selection	Issues	Ref.
ProSolv HD90	Diluent	Density (0.49 g/ml); Free Flowing	10.64-16.64	KTRON KT20 KTRON KT35	Coarse concave Coarse auger.	Powder fed too freely and filled flight of screws and flushed out too freely. Screen required to retain the powder in the screw for longer.	(22)
Colloidal Silicon Dioxide	Glidant	Density (0.04 g/ml); Cohesive; Electrostatic.	0.218-0.341	KTRON KT20	Coarse Concave	Feeder was instrumented with static eliminator to reduce material adhering to equipment. Auger screws can lead to stagnant areas within flight of screws; Fine screws cannot deliver capacity	(22)
API (not identified)	API	Density (0.61 g/ml) Free flowing.	12.48-19.51	KTRON KT20 KTRON KT35	Coarse concave Coarse auger	API build up on coarse auger screw so coarse concave used due to self-cleaning properties. No screen used due to build up.	(22)
Magnesium Stearate	Lubricant	Density (0.14 g/ml)	0.177-0.278	KTRON MT12	Coarse concave Fine Concave	Easily sheared and coats other powders and metal surfaces. Only tested with self-cleaning screws.	(22)
Crospovidone	Disintegrant	Density (0.33 g/ml)	0.480-0.750	KTRON MT12 KTRON KT20	Fine Concave	Fed easily with no issues. Potential material build up. Only tested with self-cleaning screws.	(22)
316 Fast Flo Lactose	Diluent	Density (0.58 g/ml)	Not specified	KTRON KT35	Coarse concave Fine concave Coarse auger Fine auger	Material ran for all tooling conditions and speed settings in volumetric and gravimetric mode.	(25)
Avicel PH 102	Diluent	Density (0.30 g/ml)	Not specified	KTRON KT35	Coarse concave;	Overloaded motor at highest speed setting with coarse auger screw (highest throughput) and fine screen.	(25)
Ceolus KG-802	Diluent	Density (0.21 g/ml)	Not specified	KTRON KT35	Fine concave Coarse auger Fine auger	Both coarse auger and fine auger resulted in motor overload with fine screen.	(25)
API (not identified)	API	Density (0.14 g/ml)	Not specified	KTRON KT20; Schenk Accurate AP300; Brabender FW40; Brabender FW18	KTRON (flighted auger; fine concave and core and spiral). Brabender models (Open spiral single screw)	Low bulk density of API posed issues with flighted auger and fine concave which caused increase in feeder motor torque. Only core and spiral screws could feed API which reduced machine capacity and required much operator intervention due to formation of rat holes. The KTRON KT20s rigid design posed issues. Brabender flexible frame models were more successful in feeding particular API. .	(26)