

Pills Pills Pills ...

Solid dosage forms have been used for hundreds of years, and the fact that they are still the most widespread and popular method of drug delivery today says a lot about their efficacy and acceptance. In ancient times, pills were made by mixing APIs with excipient into a soft mass, which was then divided into equal portions. The traditional pill has now been replaced by more advanced and accurate tablets, capsules and caplets, but the term 'pill' is still used colloquially to refer to any solid dosage form.

Nowadays, tablets are the most widely used solid dosage form and although tableting techniques and processes are well-established, this doesn't mean that they aren't evolving. Indeed, tablets have come a long way from simple compressed forms, with manufacturing methods now capable of producing more advanced tablets, such as those that enable controlled

release. And in the last issue of PTE, we featured an interview with researchers about the creation of a pill that can be magnetically held in an area of interest for a user-defined duration. If you missed out on this interview, you can catch up at www.pharmtech.com/magneticpills

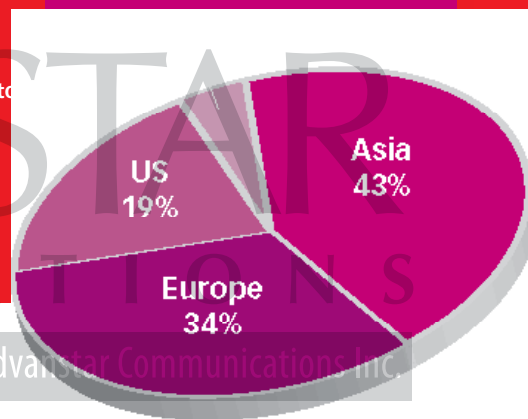
As well as ongoing innovation, there are a number of other trends impacting the industry. Firstly, there is a drive to cut costs while increasing manufacturing efficiency, which has led tableting manufacturers to seek out new systems. Secondly, there is a need to keep up with competition from developing markets, which is a particular issue for suppliers of tableting equipment — especially those in Europe and the US. According to a recent poll on www.pharmtech.com, the majority of tablet manufacturers source their equipment from Asia.

For this special tableting feature, we brought experts together to talk

about some of the current trends and innovations in the industry. The digital edition of this tableting feature, including a product showcase of tableting technologies, can be accessed at: www.pharmtech.com/ptedigital0411



From which region do you buy the majority of your tablet manufacturing equipment?



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Expert Views

Pharmaceutical Technology Europe brings together suppliers of tableting equipment and excipients to discuss the challenges, innovations and latest trends in the tableting industry.

Q What are the key drivers for change in the tableting industry?

Chris Prideaux: There are many changes affecting the tableting industry — many of which stem from those taking place in the pharma industry as a whole. The biggest drivers for change are the number of blockbusters coming off patent, and

the inexorable growth of generic drug producers and contract manufactures. Both factors place an immediate demand on suppliers of manufacturing equipment for systems offering better speed of response and better value for money. The drive to optimise growth opportunities in developing markets is also leading to greater globalisation. The relocation of facilities away from traditionally high-cost developed

markets to lower-cost developing markets means that suppliers of tableting machines and other pharma manufacturing equipment must be able to meet the needs of these markets and provide increasing levels of support.

Dale Natoli: I think the main focus of the tableting industry at the moment is on quality, and boosting productivity

and manufacturing efficiency. From a tablet compression tooling standpoint, regulatory affairs are making a stronger presence in medium and large-scale operations with regards to more stringent process controls to ensure tablet quality.

Sophie Chesnoy: Looking at the tabletting industry from the point of view of an excipient supplier, the main drivers for change will be the development of new excipients for solid dosage forms that enable better control over physical properties, ultimately improving the quality of the final product. In particular, tabletting manufacturers' needs for improved powder flowability, compressibility and lubrication are key in driving excipient innovation.

Q What are the main challenges facing tabletting manufacturers?

Prideaux: In anticipation of future patent losses, we are seeing tablet manufacturers trying to boost the productivity of their blockbusters to ensure a robust supply chain as a counter to new generic entrants. The challenge here is to increase capacity and reduce costs, without a massive investment. There are a number of solutions on the market that can help achieve this, including multi-tip tooling, die segment turrets and coatings; all of which can facilitate the speed or output of an existing tablet press. Paying greater attention to the fine detail of tooling design and the effective maintenance of both the tooling and press can also help reduce tablet press down time and increase productivity.

Globalisation and the relocation of products to alternative plants worldwide can also create problems. For instance, subtle changes in environmental conditions and material supply can hinder process replication at a new site, and there is also the challenge of training new operatives. The knowledge and support of key suppliers with global experience can be vital in supporting this process, and the speed and effectiveness of the supplier's response can be critical.

Finally, the pharma industry must juggle the margin loss from the former

blockbusters with the need to invest in new drug development. The net result of this is increased pressure to reduce cost and increase efficiency in all manufacturing operations.

Natoli: One of the major challenges for the tabletting industry is the competition that is now coming from developing, low-labour index countries. However, competition also has its benefits because it encourages innovation and process improvements. The need for reduced costs and manufacturing times has also led a number of manufacturers to use direct compression, which offers reduced costs and processing times. However, caution is required because some blends using this method result in unfavourable powders that are not suitable for tabletting.

Looking more in-depth at the tabletting manufacturing process, there are a number of common challenges that must be faced such as capping, sticking and tool binding. To overcome these issues, many tablet manufacturers have their punch or die configurations modified to be better suited for the product being compressed. This isn't a new trend as such, but is becoming more prevalent as tablet manufacturers attempt to reduce costs by minimising powder processing.

Chesnoy: The manufacturing processes for tablets can be divided into three techniques: wet granulation, dry granulation and direct compression.

With wet and dry granulation techniques, the challenges relate to the complexity of the many steps involved in obtaining a powder blend exhibiting required flowability and compressibility parameters. For the simpler process of direct compression, the main challenges are to guarantee excipient properties and control any variables.

According to a survey conducted in 2010, poor formulation design accounts for 34% of common problems encountered during tablet manufacturing, while problems in blend uniformity account for 15%.¹ This means that around 50% of the problems encountered by tabletting

manufacturers could be solved by adjusting the mechanical properties of powders, such as flowability, dilution potential and compressibility.

The remaining problems are linked to tabletting equipment. As the excipient's performances should be tested on different tablet presses, the development of a tablet press simulator could help gain a better understanding of the physical behaviour of excipients, and blends thereof, under compression. Conventional presses equipped with data acquisition systems could also provide information on compression cycles, ejection force and heckle plot analysis.

Q What has been the greatest innovation in the tabletting industry during the past few years?

Prideaux: It is difficult to single out one innovation because there have been a number that have had a significant influence on the industry, including direct compression, which is an extremely efficient process in terms of process control and tabletting parameters. In-line process inspection is another technology that has significantly impacted tablet production processes by helping to control variability. Tablet coating technologies have also developed considerably and can provide innovative solutions for drug dissolution and controlled release. From a tablet compression tooling perspective, we have seen multi-tip tooling (increasing the number of tablets produced from a single punch), die segments (increasing the number of punches in the tablet press) and tool coatings, all of which have had a positive impact on tablet manufacturing.

Natoli: The tablet compression industry has seen many innovations in recent years, such as wash/clean in place technology, product containment, exchangeable die disc and die shells, die segments and tablet-in-tablet technology, to name but a few. In my opinion, the greatest is not so much a new innovation but rather a new acceptance of an older technology: multi-tip tooling. Although multi-tip tooling has been

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used in tablet compression for over a century, it's only in the past couple of years that it has now been refined and accepted by the pharmaceutical industry. Multi-tip tooling can help manufacturers to significantly increase production; for instance, one tablet manufacturer we were working with was producing six to seven thousand tablets/min using a single tip, but became capable of producing 24 to 30 thousand tablets/min after switching to 4 tip. The number of punch tips per tool is typically related to the punch size and tablet size. Companies can contact their tooling manufacturers to find out if their product is a candidate for multi-tip tooling.

Chesnoy: The demand for reduced costs and simpler formulations has led to further development of the direct compression technique. In this technique, powder characteristics are critical. The need for improved powder properties, without having to develop a new chemical entity, has been met by the development of co-processed excipients, where several excipients are processed simultaneously to obtain synergistic effects in functionalities. A number of articles have been published that highlight the advantages of co-processed excipients for tabletting.^{2,3}

Q What features/improvements would you like to see in future tabletting methods/processes?

Prideaux: As a supplier of tablet compression tooling, we would welcome tablet press manufacturers embarking on some degree of standardisation (e.g., key positions) in line with global tooling standards across all types of tablet press. This would benefit the end users by increasing the potential for interchangeability of tooling across tablet presses and individual production sites/markets worldwide. Lubrication-free tablet presses would also help tablet manufacturers to minimise product loss caused by contamination. Finally, we would welcome innovation around the in-line monitoring of formulations prior to compression (e.g., humidity and granule size), which could do much to mitigate process variation throughout the tablet production process.

Natoli: There is a strong need for integrated temperature monitoring and controls for high-speed output tablet presses. A growing number of tablet formulas and granulations are sensitive to tablet press operating temperature and the heat generated by tablet compression.

Sensing functions would also be useful for both new and retrofit tablet presses to give feedback on whether a product has started to pick or stick on the lower punch before producing

a barrel of tablets. Also, detecting the necessary forces required to remove a tablet from the lower punch could set new guidelines to eliminate question marks over differences between development and production. Although, maybe this isn't possible!

Chesnoy: Simplification is the key word! Simplification of formulas and processes will ultimately help save time and costs.

Among compression techniques, direct compression remains the simplest technique available and requires less time and energy. On the other hand, this technique is highly demanding in the number of required excipient properties. The ideal excipient for direct compression should exhibit constant particle sizes and shapes as these have a strong influence on density and compressibility. Compactability is also affected by tablet size and weight, and the type of press used in manufacture. In the end, in-depth excipient knowledge linked to process equipment will be a win-win strategy for developing innovative excipients for the tabletting industry. **PTE**

References

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Taking a closer look at the surface



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The term 'surface analysis' covers a range of methods for abstracting information from the outermost region of a tablet or other material. This may be physical information about the surface form, particular surface features, or it may be chemical information regarding surface composition. A number of techniques are available, including mass spectrometry and X-ray photoelectron spectroscopy (XPS).

Surface analysis can be used in many aspects of tabletting, including analysing batch-to-batch cross contamination, long term stability, dissolution rate

and die sticking. Cross contamination, for instance, can be discerned from the surface contamination of tablets. Surface analysis can also be used in the fight against counterfeits. Counterfeit tablets can differ from the real thing in many ways, including packaging, formulation and processing method. Surface characterisation is relevant to all of these, but is particularly useful when the processing method is the only real point of difference. **PTE**

Read more about surface analysis at www.pharmtech.com/ptedigital0411