The future of tableting technology.

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Editorial

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Some 50 to 60 years ago, Prof. Takeru Higuchi and his coworkers laid the foundation of modern tableting technology by publishing a series of papers on the 'Physics of Tablet Compression' (1, 2). Since then there has been additional progress in tableting technology, especially to meet material and processing needs of high-speed tablet presses. However, tableting of drug substances still remains an expensive, time-consuming and labor intensive batch process consisting of multiple unit operations. Large amounts of excipients are required to overcome deficiencies of drug substances with respect to their compactibility, flow, bulk density and other attributes necessary for tableting, which make the tablet size large, particularly creating challenges with the formulation of large-dose tablets and bilayer tablets. Because of the use of multiple unit operations, any progress towards continuous manufacture of tablets to gain production efficiency has also been limited. It is expected that the situation may change in the near future due to the recent introduction of an advanced melt granulation technology in the pharmaceutical field, where drug substances are granulated with thermoplastic polymers at elevated temperatures using twin-screw extruders to improve their compactibility and processability.

Most drug substances are inherently non-compactible, i.e, their powders may not be compressed into tablets with acceptable hardness. Three common methods are generally used to process drug substances into tablets, i.e., (i) direct compression by blending active ingredients with relatively large amounts of excipients, (ii) wet granulation of drug-excipient mixtures using low- or high-shear granulators and sometimes fluid-bed granulators, and (iii) roller compaction of drug-excipient mixtures (3). Direct compression is a simple two-step process of mixing and compression. The introduction of microcrystalline cellulose in the 1960s (4) and of coprocessed excipients later (5) made direct compression of drug substances into tablets possible. However, the drug content in a tablet formulation intended for direct compression may not exceed 30-40 %, and even then many drug substances may not be directly compressed because of inadequate compactibility, poor powder flow, segregation of powders and lack of content uniformity. The

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powder flow and compactibility become special issues for poorly water soluble drugs that usually require milling into very fine powders. For these reasons, only a small fraction of currently marketed tablets are manufactured by direct compression. Both wet granulation and roller compaction are more versatile methods than direct compression. They are, however, more complex processes requiring multiple unit operations (3). These processes also require large amounts of excipients, the typical drug content being 50% or less.

In addition to wet granulation and roller compaction, melt granulation has also been investigated in the pharmaceutical field for a long time. However, it has rarely been used for large scale manufacture of tablets. In the conventional melt granulation process, drug substances are granulated with waxes, lipids, polyethylene glycols, etc., in heated high-shear granulators. The melting temperatures of the granulating agents used are usually > 50°C, but seldom exceed 90°C (6). Due to the presence of such low-melting waxy materials, the granules produced may not have desirable attributes for tableting.

In the past 3 to 4 years, there have been several reports in the literature where twin-screw extruders have been used to convert drug substances into granules or particulates providing good flow and high compactibility (7-9). The tablets produced also exhibit low friability. Lakshman *et al.* (7) mixed 90% w/w metformin HCl with 10% w/w hydroxypropylcellulose (HPC) and passed them through a twin-screw extruder at different temperatures ranging from 140 to 180°C, which were below the melting temperature of the drug substance (224 °C) but above the glass transition temperature (T_g) of HPC (130 °C). No dies were used at the end of extruder barrels to facilitate extrusion of the granules. At the granulation temperature, the drug substance remained as dry powder while the polymer converted into the rubbery state. Granules were formed because of the high shear energy imparted by the extruder to such a drug-polymer mixture. The polymer transitioned back into the amorphous state when the granules extruded from the heated barrels and cooled to the ambient room temperature. The granules were milled if, necessary, to convert them into a uniform particle size. It was postulated that the amorphous polymers formed bridges in between the drug particles in the granules and they also coated the surface of the granules, both of which created much stronger inter-particulate bonding during tableting.

Granules with excellent tabletability could be obtained with 10% w/w or less polymer. The densification of materials within the extruder barrels occurs due to pressure generated by the screw elements as well as by the restriction of flow created by the positive conveying of materials into the kneading elements. Therefore, the design and arrangement of screw elements, screw speed, feed rate, barrel temperature and torque generated within the barrel are some of the critical process variables when using twin-screw extruders for melt granulation. Depending on the needs of the drug formulation, polymers with different T_g, melt viscosity and hydrophilicity may be used during the twin-screw melt granulation. The physicochemical properties of several such polymers are reported in a series of three papers published in the present issue of this Journal.

In a separate study using the twin screw melt granulation process, Vasanthavada *et al.* (8) used mixtures of HPC and ethylcellulose (EC) at a drug substance to polymer ratio of 90:10 w/w to formulate extended release tablets of imatinib mesylate. Research thus shows that the technology can be used for both immediate and modified release tablets. Greater amounts of polymers, as well as, other excipients may be used, if necessary, to meet specific formulation needs, such as dissolution rate, bioavailability enhancement, etc.

Since relatively small amounts of excipients can be used to produce acceptable tablets, the process is especially suitable for high-dose tablets in order to keep the tablet size smaller. It is also suitable for bi-layer tablets, where it is often necessary to reduce the size of a layer to maintain the overall tablet weight relatively small. Even for a relatively low-dose tablet, the twin-screw melt granulation process would lead to cost savings as lower amounts of excipients would be needed and, due to the lower tablet weight, a particular batch size would produce more tablets. It is expected that the twin-screw melt granulation process could also result in a new generation of co-processed excipients, where currently available pharmaceutical excipients could be converted to better compactible and flowable forms by co-granulating them with suitable polymers. One concern for the process is the possible degradation of drug substances during melt granulation at high temperature. Most drug substances may, however, not be susceptible to degradation since they are granulated below their melting temperatures and additionally tend to be exposed to these temperatures only for a very short time. Even when such a possibility exists, suitable polymeric excipients may be available that can be extruded at a relatively lower temperature.

The manufacturing processes in the pharmaceutical industry have not kept pace with time (10). Pharmaceutical equipment and process capability are outdated when compared with the benchmarks of what can be achieved and what should be achievable. Although not directly comparable, pharmaceutical processes operate far below the performance and efficiency levels attained by the semiconductor and other consumer products manufacturing practices. This situation results in high manufacturing costs and possible delays in bringing the product to the market. Product failure due to suboptimal manufacturing processes may be detrimental to a pharmaceutical company. Since tableting is still, by scale, the most common manufacturing process in the pharmaceutical industry (an estimated more than 3 out of 4 dosage units taken by patients are tablets), an improvement in tableting technology could greatly benefit the industry and ultimately patients. As opposed to other granulation techniques mentioned above, melt granulation using twin-screw extruders can be automated for continuous manufacturing of tablets (11). The pharmaceutical Quality-by-Design paradigms can be adapted to the melt granulation process and each step of the process can be monitored using inline process analytical technology (PAT). There are multiple reports that melt granulation using twin-screw extruders has already been scaled up to the large commercial scale manufacture of tablets and the finished drug products are on the market.

In a recent editorial of this Journal (12), Moreton asked: "How can the chances of developing robust products be boosted?" According to him, "the answer lies in improved knowledge and understanding of excipients, APIs and unit operations involved in the manufacture of the medicinal product, and how they interact to produce robust formulations and products." The answer cannot be truer in case of the tableting technology, where it is expected that the availability of a wide array of polymeric excipients, the recent introduction of melt granulation technologies using twin screw extruders, and the interrelationship between excipients and technology will bring major changes in how tablets are formulated and produced in the future. More research is needed to ensure that such innovations are widely applied in the pharmaceutical field.

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