Pharmaceutical BIOPROCESSING

Continuous manufacturing: the future in pharmaceutical solid dosage form manufacturing

"...the continuous manufacturing concept has planted a new hope in the pharmaceutical industry to improve the process efficiency and product quality ... resulting in reduced production time and a shorter 'time to market'."

Keywords: batch manufacturing • blending • compression • continuous manufacturing • granulation • on-line real time trending • process analytical technology • process efficiency • solid dosage form

Parind Mahendrakumar Desai[1], Griet Van Vaerenbergh[2], Jim Holman[3], Celine Valeria Liew[1]

[1]GEA-NUS Pharmaceutical Processing Research Laboratory, Department of Pharmacy, National University of Singapore, 18 Science Drive 4, Singapore 117543, Singapore

[2]GEA Processing Engineering nv, Keerbaan 70, 2160 Wommelgem, Belgium

[3]GEA Process Engineering Ltd., School Lane, Chandlers Ford, SO53 4DG Eastleigh, Hampshire, UK

Paul Wan Sia Heng

Author for correspondence:
GEA-NUS Pharmaceutical Processing Research Laboratory, Department of Pharmacy, National University of Singapore, 18 Science Drive 4, 117543, Singapore

Tel.: +65 6516 2930

phapaulh@nus.edu.sg

The highly conservative pharmaceutical industry is now approaching an era of renewal, transforming from batch manufacturing to continuous manufacturing, to convert seamlessly in fast continuous sequence, raw materials into high-quality final products [1,2]. This transformation is significant, to meet demands on solid dosage forms manufacture through cost savings by simplifying processes, reduced space and energy footprints, reduce product failures and yet, provide even better quality products for patients [3,4]. Full automation allows for consistent product quality produced under 24 h production capabilities [5]. However, high initial investment cost, vagueness on the long-term capability of the manufacturing system and the uncertainty of regulatory requirements for continuously manufactured products are some initial hurdles creating reluctance to adopt this highly required transformation. Currently, the most common pharmaceutical solid dosage form, tablets are manufactured by batch manufacturing. First, active pharmaceutical ingredients (APIs) are manufactured in upstream steps which mainly involve chemical synthesis, reaction engineering, crystallization, separation and purification. Almost 70% of the upstream reaction steps are in batch mode [6]. Many companies are now trying to change these batch reactions with flow reactions to generate API with minimal losses. In the next stage, isolated APIs are further treated by different downstream steps to formulate the dosage form, tablets. In a perfect future world, fully end to end continuous manufacturing, which is also coined as homogeneous processing, will take root and terms such as upstream and downstream processing may not exist anymore [7]. Homogeneous processing requires the incorporation or development of new technologies. However, before the dream of homogeneous processing becomes a reality, a transformative transitional phase, in which heterogeneous continuous processing involving the streamlining of upstream processing and downstream processing as continuous phases, has to be initiated. GEA Pharma Systems is a leading group of companies involved in developing these continuous processing systems, particularly for downstream processing and some of their systems are discussed here to provide recent updates in this emerging area.

The downstream steps for batch manufacturing of tablets involve one of the three common methods: wet granulation, dry granulation and direct compression [7]. Blending and milling are also the parts of the downstream processes and are carried out as according to the requirements. In this aspect, recently developed downstream processing methods such as melt extrusion, thin film casting and electrospinning can be considered as continuous processing with less powder handling [8]. Major limitation to prepare tablets via batch manufacturing is the requirement of very good flowing feed materials. Wet granulation is the popular method to convert free particles into aggregates with the aim to improve flow properties, compressibility and homogeneity of materials and become suitable for high-speed tableting. Continuous twin

FUTURE SCIENCE part of fsg

Figure 1. ConsiGma™-DC, a recent development to commercially manufacture tablets by continuous direct compression.

screw extrusion process was studied by Keleb *et al.* [9] to achieve wet granulation process in a continuous mode. This continuous wet granulation via twin screw was further employed commercially in ConsiGma™ (GEA Group, Wommelgem, Belgium) system [3]. This industrial designed continuous granulation technology started with three modules: a high shear granulation module, a fluid bed dryer module and an evaluation module. This set up can be further extended by adding mixer and rotary tablet press and this completes the tableting line, thus enabling full continuous manufacturing of tablets from powders. Effect of process and material variables on granule and tablet attributes and prediction of these attributes using process analytical technology (PAT) tools, particularly Raman and near infrared (NIR) spectroscopy, were further studied by different research groups, generating a significant database for this continuous system [1–3,5,10–17]. ConsiGma systems are available as units, for research-and-development to production, and have been tested for many drug products. In direct compression method, individual API(s) and excipients are dispensed by accurate loss-in-weight systems, blended, conveyed and directly compressed, making it the simplest and most preferred approach to produce tablets. However, reasonable flow properties and good compressibility of blended feed materials are the basic requirements of direct compression. Improvement in the upstream processes to manufacture drugs and excipients with properties necessary for direct compression is a necessary consideration. For the API, particle design will be a major technical challenge, to improve bulk flow and compressibility [18] and yet, satisfy biopharmaceutical requirements. ConsiGma-DC is the recent development to commercially manufacture tablets by continuous direct compression (Figure 1). The machine line comprises of four important elements, feeding, continuous blending, compression and online measurements of critical quality attributes. This advanced machine line is the example of a compact, all-in-one tablet production line by direct compression. Close integration and coupling of feeding, blending and compression have prevented segregation problem, mostly associated with direct compression. Recently, GEA along with Colorcon and University of Gent have accomplished a systematic study to evaluate the feasibility of continuous manufacture of naproxen tablet formulation using ConsiGma-DC. NIR, employed to discern chemical content, successfully allowed on-line real time trending of blend uniformity. A clear trend between API mass flow and predicted concentration by NIR tool can be seen visually in the obtained graph (Figure 2). Overall, the study represents the success story of ConsiGma-DC and confirms the suitability of the continu-

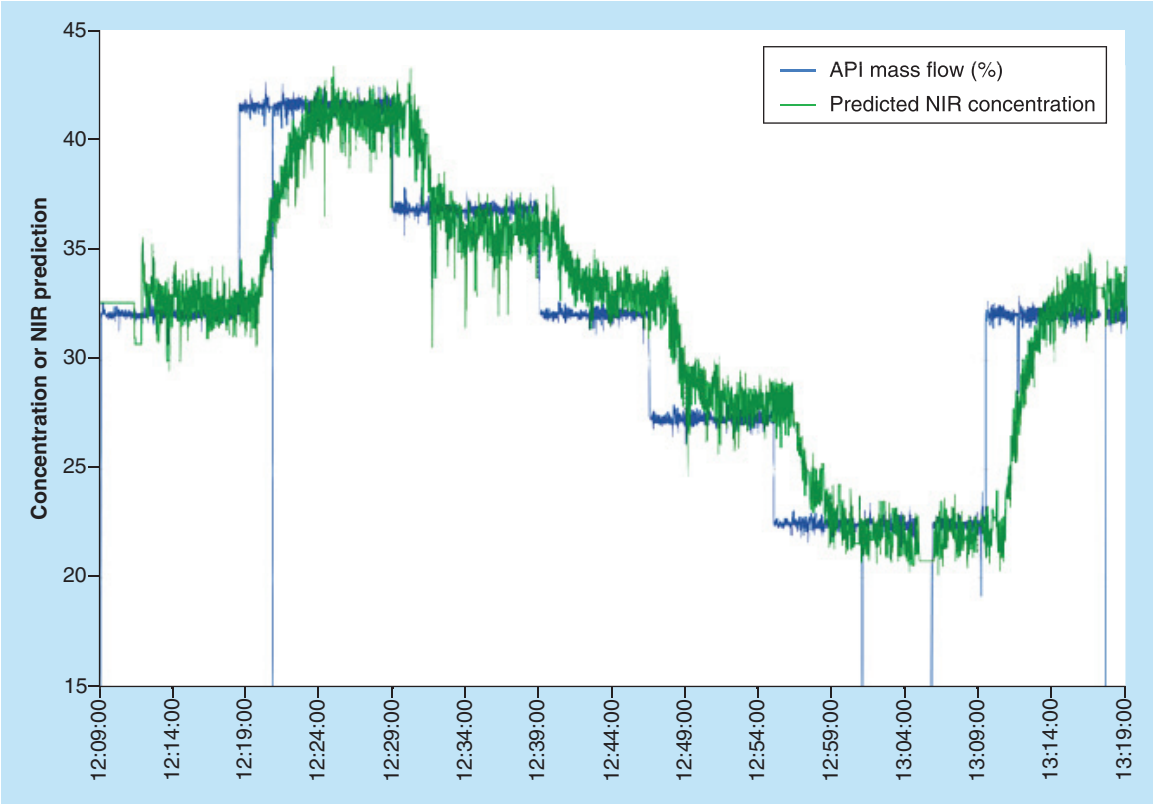

Figure 2. A sample trial showing the prediction of active pharmaceutical ingredient mass flow using a process analytical technology tool.
API: Active pharmaceutical ingredient; NIR: Near infrared spectroscopy.

ous manufacturing of tablet formulations by direct compression. Continuous manufacturing requires real-time (on-line, in-line or at-line) monitoring of intermediate or final products and therefore PAT plays a significant role in the development of continuous manufacturing systems. In the discussed examples of heterogeneous continuous manufacturing, batch size is determined by process time rather the volume of process vessel. Thus, the difficult time- and product-consuming scale up is not required for continuous manufactured pharmaceutical products. The downstream continuous processing has also minimized, if not fully eliminated, powder handing. There has been a steady increase in the number of companies that have submitted US FDA filings with continuous manufacturing steps [18]. Overall, the continuous manufacturing concept has planted a new hope in the pharmaceutical industry to improve the process efficiency and product quality. Industry's highly prevalent 'business as usual' approach has started changing, resulting in reduced production time and a shorter 'time to market'.

Financial & competing interests disclosure

Funding support is from our research grant, GEA-NUS PPRL industry grant no. N-148–000–008–001. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1 Mezhericher M. Development of drying-induced stresses in pharmaceutical granules prepared in continuous production line. *Eur. J. Pharm. Biopharm.* 88(3), 866–878 (2014).

2 Ooi SM, Sarkar S, Van Varenbergh G, Schoeters K, Heng PWS. Continuous processing and the applications of online tools in pharmaceutical product manufacture: developments and examples. *Ther. Deliv.* 4(4), 463–470 (2013).

3 Vercruysse J, Córdoba Díaz D, Peeters E *et al.* Continuous twin screw granulation: Influence of process variables on granule and tablet quality. *Eur. J. Pharm. Biopharm.* 82(1), 205–211 (2012).

4 Badman C, Trout BL. Achieving continuous manufacturing. May 20–21, 2014 Continuous Symposium. *J. Pharm. Sci.* 104(3), 779–780 (2015).

5 Fonteyne M, Soares S, Vercruysse J *et al.* Prediction of quality attributes of continuously produced granules using complementary pat tools. *Eur. J. Pharm. Biopharm.* 82(2), 429–436 (2012).

6 Yadav VG, Stephanopoulos G. Metabolic engineering: The ultimate paradigm for continuous pharmaceutical manufacturing. *ChemSusChem* 7(7), 1847–1853 (2014).

7 Byrn S, Futran M, Thomas H *et al.* Achieving continuous manufacturing for final dosage formation: challenges and how to meet them. May 20–21, 2014 Continuous Symposium. *J. Pharm. Sci.* 104(3), 792–802 (2015).

8 Brettmann BK, Cheng K, Myerson AS, Trout BL. Electrospun formulations containing crystalline active pharmaceutical ingredients. *Pharm. Res.* 30(1), 238–246 (2013).

9 Keleb EI, Vermeire A, Vervaet C, Remon JP. Continuous twin screw extrusion for the wet granulation of lactose. *Int. J. Pharm.* 239(1–2), 69–80 (2002).

10 Mortier STFC, Van Hoey S, Cierkens K *et al.* A GLUE uncertainty analysis of a drying model of pharmaceutical granules. *Eur. J. Pharm. Biopharm.* 85(3 Pt B), 984–995 (2013).

11 Vercruysse J, Delaet U, Van Assche I *et al.* Stability and repeatability of a continuous twin screw granulation and drying system. *Eur. J. Pharm. Biopharm.* 85(3 Pt B), 1031–1038 (2013).

12 Fonteyne M, Gildemyn D, Peeters E *et al.* Moisture and drug solid-state monitoring during a continuous drying process using empirical and mass balance models. *Eur. J. Pharm. Biopharm.* 87(3), 616–628 (2014).

13 Fonteyne M, Arruabarrena J, de Beer J *et al.* NIR spectroscopic method for the in-line moisture assessment during drying in a six-segmented fluid bed dryer of a continuous tablet production line: Validation of quantifying abilities and uncertainty assessment. *J. Pharm. Biomed. Anal.* 100, 21–27 (2014).

14 Yu S, Reynolds GK, Huang Z, De Matas M, Salman AD. Granulation of increasingly hydrophobic formulations using a twin screw granulator. *Int. J. Pharm.* 475(1–2), 82–96 (2014).

15 Fonteyne M, Correia A, De Plecker S *et al.* Impact of microcrystalline cellulose material attributes: A case study on continuous twin screw granulation. *Int. J. Pharm.* 478(2), 705–717 (2015).

16 Vercruysse J, Burggraeve A, Fonteyne M *et al.* Impact of screw configuration on the particle size distribution of granules produced by twin screw granulation. *Int. J. Pharm.* 479(1), 171–180 (2015).

17 Vercruysse J, Peeters E, Fonteyne M *et al.* Use of a continuous twin screw granulation and drying system during formulation development and process optimization. *Eur. J. Pharm. Biopharm.* 89, 239–247 (2015).

18 Page T, Dubina H, Fillipi G *et al.* Equipment and analytical companies meeting continuous challenges May 20–21, 2014 continuous manufacturing symposium. *J. Pharm. Sci.* 104(3), 821–831 (2015).