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DRY POWDER PRINTING TECHNOLOGY: A POSSIBLE DOSING APPROACH FOR SOLID DOSAGE FORMS OF PERSONALIZED MEDICINE

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ABSTRACT: A traditional medication is generally designed for a heterogeneous population of patients admitted with a same or similar symptom. The main disadvantages of such traditional drug products, are the single disease treatment and the fixed dose that make it not suitable to specific groups of patients, such as children, the aged and drug-susceptible patients. Personalized medicine, as a technological advancement, can promise all prediction, prevention and treatment of disease that are targeted to individual patients' need. Solid dosage forms, popular due to their advantages comparing with liquid forms, were produced by a new dosing approach using a dry powder drop-on-demand printing technology. Capsule filling with inhalation grade lactose demonstrated the potential of this technology to be applied in the production of personalized medicine.

CHALLENGES IN MODERN PHARMACEUTICAL INDUSTRY

Modern pharmaceutical industry has developed rapidly. In 2011, the annual profit of the pharmaceutical market in Europe was more than €200 billion (European Federation of Pharmaceutical Industries and Associations, 2013) and only in the UK, the pharmaceutical industry generated a trade surplus of £7 billion which was greater than any other industrial sector (Association of the British Pharmaceutical Industry, 2012). The healthcare policies and the development of advanced medicine manufacturing methods promote an improved medicines availability and affordability in either developed or developing countries (Cameron et al., 2011; World Health Organization, 2008). Hence, there is no doubt the pharmaceutical industry will keep developing extremely fast and being one of the major industries for human beings.

However, not only pharmaceutical companies, but also patients and the society are currently facing more challenges and having more expectations (Figure 1 Challenges in modern pharmaceutical industry Figure 1). A serious problem is the wrong dose taken by patients carelessly or reluctantly. Poisoning, which is the cause of over 70000 of hospital admissions in the UK, is usually due to the medicines taken in overdose (Bennett, P. N. & Brown, M.J., 2003). Although about 5% of instances were self-poisoning, inaccurate prescribed drugs or non-prescribed analgesics had led to over 90% of the poisoning instances in England and Wales. Young children, usually under 5 years of age, may swallow drugs by accident because of their curiosity about medications. And the lack of access to suitable medicines for young children has led health-care providers and caregivers to estimate the dose by breaking tablet into quarters and halves, crushing tablets or opening capsule (Finney, 2011). Another problem is the medicine waste: for example in the UK, used, partially used

or unrecyclable medication leads to as much as £300 million waste every year (National Health Service, 2012). It was found that most of healthcare payers only use part of medicine products, which may contains tens of pills or tablets. Besides, rising customer expectation on pharmaceutical products is other challenge for the industry. Healthcare payers expect new products that are clinically and economically better than the existing ones, such as multifunctional medicines. Older or disable patients prefer to more convenient pill or capsule which contains all essential substances.

Figure 1 Challenges in modern pharmaceutical industry

In the past decades, pharmaceutical companies, associations and researchers have tried their best to relieve these stresses in pharmaceutical industry: The International Committee of the Red Cross (ICRC) recommended to use four methods to minimize medicine waste: reducing the amount of waste at source, purchasing policy geared to minimizing risks, product recycling and stock management (The International Committee of the Red Cross, 2011). GlaxoSmithKline, the largest pharmaceutical company in the UK, did very well on medicine waste management that approximately 82% of their waste were reused or recycled in 2011. Another inspiring news was that tens of essential medicines, include Tylenol, Motrin, calcium and vitamins, have already produced in also child size, to reduce the possibility of potential accidental poisoning and overdose. However, these improvements and solutions are high cost ones, which are only possible to the largest pharmaceutical companies in the world. Besides, these improvements cannot satisfy all the expectations from both healthcare payers and pharmaceutical companies in a relatively short period, for example, 5 years. Hence, most of challenges are still blocking the development of pharmaceutical industry, as they have not yet been relieved or solved in very suitable and economical ways.

PERSONALIZED MEDICINE

Personalized medicine or PM, as a technological advancement that enables practitioners to identify and treat individual patients based on unique characteristics, is one of the most promising products in pharmaceutical industry (GlaxoSmithKline, 2012; Pucheril& Sharma, 2011; Personalized Medicine Coalition, 2011; Salari et al., 2012). Generally, it proposes the customization of healthcare with medical decision, practices and products tailored to the individual patient and mainly has three potential applications: pharmacogenomics, cancer management and customized drug products. Pharmacogenomics is the application of personal genomics to clinical medicine (Salari et al., 2012) and cancer management includes testing in cancer cells, defining prognosis and suggesting the most likely-to-succeed treatment options for individual patients (Leibman, 2012; Mansour& Schwarz, 2008). Customized drug products generally contain several drug substances in particular respective doses, specifically for individual patients. They are usually prescribed by physicians who have wide discretion and then the prescriptions can be custom-produced. Since customized drug product is more based on simpler characteristics such as age, weight and drug sensitivity, instead of complex genetic information, it has the higher possibility to be achieved in the next several years. With the help of an individual database, the symptom, the efficacy and bio-availability of medicines and the prescription record of a patient can always be tracked and studied and thus improve the quality and the safety of treatment.

Hence, patients, the pharmaceutical industry, and society can all be the beneficiaries from the developments of customized drug products: Because of the precisely selected drug substance, the medicine waste can be easily managed within manufacturing, sale and patient healthcare, and the risk of overdose can be significantly reduced. Besides, customized poly-pills and child size medicine, both the potential products of such customized drugs, can highly contribute to the development of medicinal products for the aged, the disable and the young patient healthcare respectively (van't Veer&Bernards, 2008). Although there are truly tens of compounding pharmacies existing in some of the Western countries, particularly in the United Kingdom and the United States (PharmWeb, 2013), the extremely high costs of raw drug material, operating, labor and pharmaceutical machines are still the barriers for the development of customized drug product. Thus, both medicine specialists and engineering researchers have tried to discover the alternative methods and applications to produce personalized healthcare products, for example, the use of printing technologies (Figure 2). The first solid free-form fabrication printer, which can form tablets using pharmaceutical-grade materials, was designed and produced by Massachusetts Institute of Technology (MIT) scientists in 1997 (Massachusetts Institute of Technology News, 1997). Their drug printer operates by dropping drug doses onto thin layers of fine powder. The tablet was finally formed when the doses were bound layer by layer with pharmaceutical-grade binder. They reported hundreds of pills could be produced at one time and the printing forms with higher dosage would be possible as the drug suspensions could overcome drug solubility limits and uni-axial compression could reduce tablet volume. In University of Glasgow, Lee Cronin and his team is developing a revolutionary new technique using 3D printer to print special drugs (The Guardian, 2012). The principal of the drug printing technique is to print the last reagent first and then build other chemical layers above, finally adding a liquid at the top; this liquid flows into the layer in sequence and until at the bottom, the final drug product will be the same as prescription.

Figure 2 The scheme of producing multi-substances capsules and tablets by printing technology

DRY POWDER DOSING AND PRINTING

Solid dosage forms are prior consideration in personalized drugs. First of all, chemicals and drugs are most stable as dry powders. They are packaged, transported, administered, and stored more easily than are drugs formulated in solutions or suspensions. Secondly, solid dosage forms, such as tablets and capsules, possess more chemical and physical stability and less undesirable taste when substances are in solid form than when in solution. Moreover, when it was packaged in blister packs can also enhance the stability of tablets. Besides, more accurate dosing is facilitated with dosage forms furnished as individual units, such as tablets, capsules, and divided powders. At last, controlled release is much easier to achieve with solid dosage forms than with liquids. Although the solid dosage forms have these advantages comparing with liquids, the challenge always exists in industry to dose powder material accurately and reproducibly into the capsules, blisters or reservoir containers of drugs especially when each capsule or blister is required to be filled with micro mass ingredients. Currently available powder dispensers have a few limitations in dispensing such small amounts of micron-sized powders, e.g. expensive, time consuming and require high levels of operational complexity. Most importantly, it is the drug content uniformity in each dosage which assures consistent therapeutic benefits in patient (Williams et al., 2002).

To produce solid dosage forms of personalized medicine, a drop-on-demand technology was developed by author's group, which can dispense dots of either one substance or multiple substances very precisely. In contrast with continuous jet printing which delivers a fluid under pressure, dry powder printing technology only forms droplets of dry powders when an electrical pulse signal is applied. A piezoelectric transducer is excited by this signal to provide a switchable vibration to the dry powder. The induced powder flow occurs in the vibratory hopper which can accurately dose powder material into micro-vessels. The dose mass of powders ranged from a few milligrams to several grams is able to be achieved with less than 2% error (Li & Yang, 2012). Also, a computer controlled 3D printing platform is applied to assist the multiple solid dosages printing for personalized drugs. With this printing technology, the release time of drug pills can be easily controlled by defining the placement of drops in the mould, and therefore provide a better match the pharmacology of drug absorption. A three ingredients capsule filling has been demonstrated with dyed inhalation grade lactose powder shown in Figure 3. The ratio of three components yellow, green and red was 1:1:2 in which the amount of component yellow/green was 1 ± 0.1 mg.

Figure 3 Three ingredients capsule samples fabricated by dry powder printing platform, a) side view of capsules in a same row; b) single printed capsule; c) top view of 96 capsules printed on the platform

The feasibility of dry powder printing technology has been demonstrated in the production of solid dosage forms. It provides the possibility of producing personalized medicine in the near future, and would lead to more rapid development timeframes, from early stage clinical trials to on-line production at a reduced cost.

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