

THE FUTURE OF DOSAGE FORM: A BRIEF REVIEW**Pal Sandhya*, Garg Garima, Sharma Anjana**

Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology,
Baghpat Bypass, Delhi Roorkee Highway, Meerut- 250005, Uttar Pradesh, India.

Article Received on
10 July 2015,

Revised on 03 Aug 2015,
Accepted on 26 Aug 2015

***Correspondence for
Author**

Pal Sandhya

Department of
Pharmaceutical
Technology, Meerut
Institute of Engineering and
Technology, Baghpat
Bypass, Delhi Roorkee
Highway, Meerut- 250005,
Uttar Pradesh, India.

ABSTRACT

Today's medication is mostly targeted to the indication, not to the individual patient or consumer and his specific needs. Pharmaceutical industry is moving from specialty drugs targeted to specific patient groups and to personalized medicines. The foundation of the future for the pharmaceutical lies in combining traditional therapeutics with devices. In the present article emerging technologies, such as bioelectronic medicines and 3D printing of pharmaceuticals, ink jet printing and biosimilars are discussed through which customization is taking root in pharmaceutical dosage form designing.

KEYWORDS: Personalized medicines, Bioelectronic medicines, 3D printing of pharmaceuticals, Inkjet printing, Microchips, Biosimilars.

1. INTRODUCTION

The pharmaceutical industry is undergoing certain changes its focus is now moving to specialty drugs targeted to specific patient groups or in other words towards personalized medicines. Today's medication is mostly targeted to the indication, not to the individual patient or consumer and his specific needs. A customized medication approach is based on a genetic and phenotypic assessment at affordable costs, looking into the human body and predicting the likelihood of possible health problems throughout life. In a report, FDA notes that the term "personalized medicine" is often described as providing "the right patient with the right drug at the right dose at the right time", but more broadly, "personalized medicine may be thought of as the tailoring of medical treatment to the individual characteristics, needs, and preferences of a patient during all stages of care, including prevention, diagnosis, treatment, and follow-up".^[1]

Personalized medicine involves -- a diagnostic device and a therapeutic product-- which helps in improving patient outcomes. A vast variety of medical devices can be used in a personalized approach to improve patient outcomes. These medical-device therapies can be used for specific patient characteristics, such as patient anatomy (e.g., size), physiology (e.g., nervous and cardiovascular systems, metabolism, and reproduction) and environment (e.g., intensive care unit, home use). Physiological sensors may predict treatment responses such as three-dimensional (3D) printing, to create personalized medical devices based on patient's anatomy.^[1]

The convergence of traditional therapeutics with devices provides the base for the future pharmaceutical. Customization can be achieved through prominent technologies, such as bioelectronics medicines and 3D printing of pharmaceuticals, through select investment by companies, venture-capitalists, researchers.

2. EARLY EXAMPLES OF PERSONALIZED MEDICINES^[1]

1907: Reuben Ottenberg reports the first known blood compatibility test for transfusion using blood typing techniques and cross-matching between donors and patients to prevent hemolytic transfusion reactions.

1956: The genetic basis for the selective toxicity of fava beans ("favism") and the antimalarial drug primaquine is discovered to be a deficiency in the metabolic enzyme, glucose-6-phosphate dehydrogenase (G6PD).

1977: Cytochrome P450 2D6, a polymorphic metabolizing enzyme, is identified as the culprit for causing some patients to experience an "overdose" or exaggeration of the duration and intensity of the effects of debrisoquine, a drug used for treating hypertension.

3. POSSIBILITIES IN FUTURE DOSAGE FORM

3.1 Microchip drug delivery

Much Research has been going to find ideal system for drug delivery within body. Drug delivery is very important aspect of medical treatment and finding a drug delivery device that is capable of controlled or continuous release of wide variety of drug is of great advantage. Polymeric device provide control release of drug over a period of time. The problem with this device sometime polymer degrades too fast in body.^[2]

Microchip drug delivery is the most wonderful system of delivering the drug for a great span of time without the intervention of patient to whom it is fixed. Microchip controls both the

rate and the time release of molecule.^[2] This allows release of wide variety of molecule in either continuous or pulsatile manner. The device consists of substrate containing multiple reservoirs is capped with conductive membrane (gold) and wired with final circuitry controlled by microprocessor. Reservoir is etched into substrate using either chemical etching or ion beam etching techniques. Hundreds to thousands reservoirs can be fabricated on a single microchip using micro-fabrication.^[2]

A microchip system has the ability to store a large number of drugs or chemicals, control the time at which release begins, and control the rate at which the chemicals are released. Drug delivery device is capable of controlled, pulsatile or continuous release of a wide variety of drugs that can be safely implanted inside the body. The microchip could be integrated with a tiny power supply and controlled by a microprocessor, remote control, or biosensors.^[2] The molecules to be delivered are inserted into reservoir by injection. The reservoir can contain multiple drugs or other molecule in variable dosages. The filled reservoirs can be capped with material that degrade or allow the molecule to diffuse out of reservoir over time or materials that oxidize and dissolve upon application of electric current. Release from an active device can be controlled by a preprogrammed microprocessor it is used in diabetes, Parkinson's disease, congestive heart failure, anti coagulation.

3.1.1 The design approach of microchip

3.1.1.1 The substrate

Any material that can serve as a support is suitable for etching and is impermeable to the molecules to be delivered and to the surrounding fluids may be used as a substrate. For this *in vivo* application, biocompatibility should be considered. Non compatible materials, can also be enclosed within biocompatible materials like poly ethylene glycol. One example of strong, non- degradable, easily etched substrate that is impermeable to the delivered chemicals and non-degradable to the surrounding environment within the body is silicon.

3.1.1.2 Release system

The design of a release system depends on treatment required by the patient whether it is a continuous or pulsed release. Drug delivery can be achieved by a passive or active release system. In the passive system, drugs diffuse through a membrane by the degradation of the substrate. Active systems are preferred due to a more predictable release profile. The exact time release and amounts of drug can then be controlled.

3.1.1.3 Reservoir caps

The reservoir caps consist of a thin film of conductive material. Any conductive material that can oxidize and dissolve in solution upon application of an electric potential can be used for fabrication of the anodes and cathodes. Gold is chosen as the model membrane material because it is easily deposited and patterned, has a low reactivity with other substances and resists spontaneous corrosion in many solutions over the entire pH range.^[3] Presence of small amount of chloride ion creates an electric potential region which favors the formation of soluble gold chloride complexes.^[4] Holding the anode potential in this corrosion region enables reproducible gold dissolution. Potentials below this region are too low to cause appreciable corrosion, whereas potential above this region result in gas evolution and formation of a passivating gold oxide layer that causes corrosion to slow or stop.^[3]

3.1.1.4 Control circuitry and power source

The control circuitry consists of a timer, de-multiplexer, microprocessor or an input source. The input source can either be a memory source, remote control device or a biosensor. A thin film micro battery can be used as power source. These can pattern on device.

3.1.1.5 Reservoir filling

Three-dimensional printing is capable of fabricating structures by ink-jet printing liquid binder onto loose, fine powder. The printing pattern can be obtained from computer aided-design model (CAD). Inkjet printing in combination with a computer-aided alignment apparatus is capable of depositing as little as 0.2 ml of liquid or gel solution of known concentration into each reservoir. The volume of reservoir can be controlled by specifying the appropriate print head to deposit a predetermined amount of binder. The drug is pushed out of nozzle as the vapor bubble.

3.2 3D printing of pharmaceuticals

Three-dimensional (3D) printing is a manufacturing method in which objects are made by fusing or depositing materials in layers to produce a 3D object. This process is also referred to as additive manufacturing (AM), rapid prototyping (RP), or solid free-form technology.^[5] Some 3D printers are similar to traditional inkjet printers; however, the end product differs in that a 3D object is produced. 3D printing is expected to revolutionize medicine and other fields, not unlike the way the printing press transformed publishing.^[6] “3D printing is probably the most innovative idea in the pharmaceutical industry since decades,” says Scheffler. “It will change our lives and will play a major role, in fact, in literally all

industries. New formulations with existing and approved excipients and ingredients will benefit from these creative new ways because we can customize medicine to each individual patient. The effect is less waste, less costs, and less complexity for patients”.

Charles Hull invented 3D printing, which he called “stereolithography,” In the early 1980s. Stereolithography uses a .stl file format to interpret the data in a CAD (Computer aided designing) file, allowing these instructions to be communicated electronically to the 3D printer. Along with shape, the instructions in the.stl file may also include information such as the color, texture, and thickness of the object to be printed.^[7]

Inkjet and powder-based printing were the primary printing technologies used for drug development and fabrication. These printing technologies have certain advantages, such as precise control of droplet size, high reproducibility, complex drug-release profiles, and personalized medication therapy. The printable dosage forms on paper may be easier to deliver than powder-based printed forms. Medications with narrow therapeutic indices or with a higher likelihood to be influenced by genetic polymorphisms may be the first to be printed via this technology.^[8]

3.2.1 Advantages of 3D printing^[9]

1. Custom 3D printed dosage form & drug delivery devices
2. Personalized drug dosing
3. Unique dosage forms
4. Complex drug-release profile

3.2.2 Custom 3D printed dosage form & drug delivery devices^[9]

1. Precise control of droplet size and dose, high reproducibility, and the ability to produce dosage forms with complex drug release profiles.
2. Through the use of 3D printing technology, drug manufacturing processes could also be standardized to make them viable.
3. 3D printing technology is important in the development of personalized medicine.

3.2.3 Personalized drug dosing^[9]

1. Personalized 3D-printed drugs benefit patients having pharmacogenetic polymorphism or who use medication with narrow therapeutic indices.
2. Dose could be adjusted based on clinical response by using 3D printing technology.

3. 3D printing has the potential to produce personalized medicines in entirely new medicines such as pills that include multiple active ingredients, either as a single blend or as complex multilayer or multireservoir printed tablets.
4. Patients who have multiple chronic diseases could have their medications printed in one multidose form that is fabricated at the point of care.
5. Accurate, personalized dose of multiple medications in a single tablet could potentially improve patient compliance.

3.2.4 Complex drug-release profile^[9]

1. 3D printers can print binder onto a matrix powder bed in layers typically 200 micrometers thick creating a barrier between the active ingredients to facilitate controlled drug release.
2. 3D-printed dosage forms can also be fabricated in complex geometries that are porous and loaded with multiple drugs throughout, surrounded by barrier layers that modulate release.
3. Implantable drug delivery devices with novel drug-release profiles can also be created using this technology.
4. Dexamethasone has been printed in a dosage form with a two-stage release profile.
5. Levofloxacin has been 3D printed as an implantable drug delivery device with pulsatile and steady-state release mechanisms.

4. Biosimilars

A biosimilar medicinal product is a biological medicine which is similar to a “reference medicinal product” that has already been authorised for use. A biosimilar medicinal product and its reference medicinal product are expected to have the same safety and efficacy profile. Biosimilar medicinal products are authorised either for all or selected indications of the reference medicinal product. The development and the manufacturing process of biosimilar medicinal products are more complex and expensive than generics of chemical (small molecule) products.^[10]

However, the process of introducing a biosimilar to an innovator product is far more complex than the relatively straightforward process of introducing a generic equivalent to an innovator product based on a new chemical entity. Therefore, unlike generic pharmaceuticals, it is impossible to generate the same or identical copy of an innovator product. In this way, biosimilars are “similar but not the same” or in other words biosimilars are “the twin but not

the clone” to the original biologic innovator product.^[11] Therefore the field of biosimilars presents several important challenges, including.

1. Verification of the similarity,
2. The interchangeability of biosimilars and innovator products,
3. The possible need for unique naming to differentiate the various biopharmaceutical products,
4. Regulatory framework,
5. Intellectual property rights, and
6. Public safety,
7. Commercial opportunities as well as guidelines to assist manufacturers in product development.

4.1 Biosimilar products^[11]

Table 1: Biosimilar products

Biosimilar	Reference	Approval/Rejection year
Omnitrope	Somatropin	2006*
Valtropin	Somatropin	2006*
Binocrit	Epoetin alpha	2007*
Epoetin alpha	Epoetin alpha	2007*
Abseamed	Epoetin alpha	2007*
Silapo	Epoetin zeta	2007*
Retacrit	Epoetin zeta	2007*
Filgrastim	Filgrastim	2008*
ratigrastim	Filgrastim	2008*
Biograstim	Filgrastim	2008*
Tevagrastim	Filgrastim	2008*
Filgrastim hexal	Filgrastim	2008*
Zarzio	Filgrastim	2009*
nivestim	Filgrastim	2010*
Alpheon	roferon-A	2006**
Human insulin	Humulin	2007**

*Notes: *Approved, **rejected*

4.3 Regulation aspects of biosimilars

A generic drug is a much less expensive copy of an innovator Drug product. Generics can be produced when the patent on a drug has expired, for drugs which have never held patent, in countries where a patent(s) is/are not in force, and where the generic companies certify that the branded companies' patents are either invalid, unenforceable, or will not be infringed. Generic drug manufacturers apply for marketing approval of generic drugs under the

abbreviated New Drug Application (ANDA) pathway established by FDA. Moreover, generic drug applications are termed “abbreviated” because they are generally not required to innovator products. These differences imply that biosimilars should not be approved and regulated in the same way as conventional generic drugs.

The regulatory pathway for approval of biosimilars is more complex than for the generic innovator product because the design of a scientifically valid study to demonstrate the similarity of a highly process-dependent product is not easy. Further, the analytical tests currently available are not sophisticated enough to detect the slight but important structural differences between innovator and biosimilar products. Modest differences may have clinical implications and pose a significant risk to patient safety. Therefore, it is considered necessary that biosimilars must be assessed for clinical efficacy and safety by valid preclinical and clinical studies before marketing approval.

REFERENCES

1. Rockville, M.D., Paving the Way for Personalised Medicine: FDA's Role in a New Era of Medical Product Development, FDA., 2013.
2. D. Bhowmik , H. Gopinath, B. P. Kumar, Microchip drug delivery – New era of drug delivery system, *The Pharma Innovation.*, 2012; 1: 10.
3. Santini, J.T., M.J. cima & R. Langer, A controlled release microchip, *Nature.*, 1999; 397: 335-338.
4. Frankenthal, R.P. & Siconolfi, D.J., The anodic corrosion of gold in concentrated chloride solutions, *Journal of electrochemical society.*, 1982; 129: 1192-1196.
5. J. Banks, Adding value in additive manufacturing: Researchers in the United Kingdom and Europe look to 3D printing for customization, *IEEE Pulse.*, 2013; 4(6): 22–26.
6. C. Schubert, MC van Langeveld, LA Donoso, Innovations in 3D printing: a 3D overview from optics to organs, *Br J Ophthalmol.*, 2014; 98(2): 159–161.
7. Gross, BC, J.L. Erkal, S.Y. Lockwood, Evaluation of 3D printing and its potential impact on biotechnology and the chemical sciences, *Anal Chem.*, 2014; 86(7): 3240–3253.
8. I. D. Urgan, L. Chiu, A. Pierce, Three-dimensional drug printing: a structured review, *J Am Pharm Assoc.*, 2013; 53(2): 136-144.
9. C. Lee, M.S. Ventola, Medical Application for 3D Printing: Current and Projected Uses, *P&T Community*, 2014; 39(10): 704-711.

10. European Commission, What you need to know about- Biosimilar medicinal products, Consensus Information Paper., 2013.
11. B. S. sekhon, V. Saluja, Biosimilars: an overview” Dove medical press Ltd. Biosimilars, 2011; 1: 1-11.