European Journal of Pharmaceutical Sciences 123 (2018) 1–9

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Unique laser coding technology to fight falsified medicines

K. Ludasi[a], T. Sovány[a], O. Laczkovich[a], B. Hopp[c], T. Smausz[b,c], G. Regdon Jr.[a,*]

[a] Institute of Pharmaceutical Technology and Regulatory Affairs, University of Szeged, Eötvös utca 6, 6720 Szeged, Hungary
[b] MTA-SZTE Research Group on Photoacoustic Spectroscopy, University of Szeged, Dóm tér 9, 6720 Szeged, Hungary
[c] Department of Optics and Quantum Electronics, University of Szeged, Dóm tér 9, 6720 Szeged, Hungary

ARTICLE INFO

Keywords:
Falsified medicines
Identification
Anti-counterfeiting
Laser marking
Unique laser coding
Safety

ABSTRACT

Based on WHO statistics, counterfeit medicines represent 10% of the global drug trade. According to Directive 2011/62/EU as regards the prevention of falsified medicines from entering into the legal supply chain, a unique identification should be put on each box of drugs to be able to track and trace them. The objective of this study is to develop a technology to mark an individual traceability code directly on the surface of the tablet. By using this technique, anyone with a camera-enabled phone and a suitable application installed should be able to authenticate these drugs. By marking the medicine's surface, patients could be protected from fake drugs.

The aim of the present work was to study how different types of lasers affect the film coating of the tablet during the laser marking intervention.

To sum up, the present findings may contribute to efficient and reliable laser marking solutions in the unique identification procedure. Based on our measurement results, it can be stated that the excimer UV laser is clearly the most suitable marking instrument for anti-counterfeiting coding on solid coated tablet form as this caused the least amount of chemical degradation of the polymer film.

1. Introduction

In the interest of avoiding misunderstanding, it is important to remark that the expression counterfeit medicine used in this article comprises the WHO's definitions for **substandard** (authorized medical products that fail to meet either their quality standards or specifications, or both), **unregistered** (that have not undergone approval by the National or Regional Regulatory Authority for the market in which they are distributed), and **falsified** (that deliberately misrepresent their identity, composition or source) medical products (WHO, 2018).

Counterfeit drugs pose a great threat for health and they cause serious social and economic damage. Based on WHO statistics, it is estimated that 1 in 10 medical products is substandard or falsified in low- and middle-income countries where health systems are weak or non-existent (WHO, 2018). The most frequently falsified medicines in wealthy countries were lifestyle medicines, such as hormones, steroids and antihistamines. In developing countries, they included medicines used to treat life-threatening conditions such as malaria, tuberculosis and HIV/AIDS (European Medicines Agency, 2018).

It is threatening that medicines purchased over the Internet from sites that conceal their actual physical address are counterfeit in over 50% of cases (UNICRI, 2012; WHO IMPACT, 2006).

A culture of self-diagnosis and self-prescribing has led to the emergence of thousands of unregulated websites providing unsupervised access to substandard and falsified medical products. Unregulated websites, social media platforms, and smartphone applications can also be direct conduits of counterfeit medical products (WHO, 2018). Patients across the world put their health, even life, at risk by unknowingly consuming fake drugs or genuine drugs that have been badly stored or that have expired (Interpol, 2013).

Responsible governments prohibit falsified medicines under national law but remain vulnerable to organized criminals doing business in countries where laws or enforcement are lax—30% of countries have little or no medicine regulation according to WHO (Attaran et al., 2012).

Globally, there are around 30,000–35,000 online pharmacies. 96% of these operate illegally. They do not comply with regulatory and safety requirements and they may sell prescription drugs without a valid prescription. On average, 20 online pharmacy websites are created each day (CSIP, 2016).

Falsified medicines in the legal supply chain are less prevalent in the EU, but this trend seems to be on the rise. 2 cases reported in 2012 vs. 12 in 2013 and 15 in 2014 (European Commission Staff Working Document, 2015). For example, in 2014 falsified vials of the cancer treatment Herceptin (trastuzumab) were stolen in Italy, manipulated and later reintroduced illegally into the legal supply chain in some

* Corresponding author.
E-mail address: geza.regdon@pharm.u-szeged.hu (G. Regdon).

https://doi.org/10.1016/j.ejps.2018.07.023
Received 15 March 2018; Received in revised form 18 June 2018; Accepted 9 July 2018
Available online 12 July 2018
0928-0987/

countries (European Medicines Agency, 2014; Sukkar, 2014).

A European Union Intellectual Property Office (EUIPO) report shows that fake medicines cost the EU pharmaceutical sector EUR 10.2 billion (4.4% of sales) each year. This is a direct estimate of sales lost by legitimate manufacturers and wholesalers of medicines in the EU due to counterfeiting. Moreover, 37,700 jobs and EUR 1.7 billion of government revenue are lost annually (household income taxes, social security contributions and corporate income taxes) (Wajsman et al., 2016).

The links between drug counterfeiting and other forms of crime are proven both by the methods used and the nature of the products that are regularly seized. Counterfeiting is a world-wide problem. Traffickers have a single motivation: extreme profitability. In the study report written by Eric Przyswa he has given an example: according to the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), for $1000 invested, the trafficking of counterfeit currency or of heroin would bring a return of $20,000, of counterfeit cigarettes $43,000, and in the case of counterfeit drugs, the return would be between $200,000 and $450,000. Counterfeit drugs would therefore be 10 to 25 times more profitable than the trafficking of narcotics. The major distribution vehicle is the Internet, which is decentralized and anonymous. The malleability and permanent interconnection of networks seem to offer genuine opportunities for illicit trafficking. (A Royal Pharmaceutical Society Publication, 2014; IRACM, 2013; Przyswa, 2013).

According to Directive 2011/62/EU as regards the prevention of falsified medicines from entering into the legal supply chain, a unique identification should be put on each box of drugs (The European Parliament and the Council of the European Union, 2011). The new Delegated Regulation 161/2016/EU shall enter into force from 9 February 2019, which, besides serialization requirements, demands additional anti-tampering devices for drug packaging. In Europe pharmaceutical manufacturers who distribute their products must, in the future, assign prescription medications with a serial code as a unique identification feature, save this serial number and transfer it to a Europe-wide database under the tightest security requirements. The security code specified by the EU is a 2D data matrix code that ensures traceability along the entire supply chain (European Comission, 2016).

Our team would like to extend this process by working on the development of a technology to mark an individual traceability code directly on the surface of the tablet. Anyone with a camera-enabled phone and a suitable application installed on it should be able to authenticate these drugs. Also, as in certain Member States the persons authorized or entitled to supply medicinal products to the public are allowed to open a pack of a medicinal product in order to supply part of that pack to the public, it is necessary to verify those drugs in question, too (A Royal Pharmaceutical Society Publication, 2017; European Comission, 2016). We plan that our development with on-product marking would help to verify each pill even in the absence of original packaging.

The ideal mark for medical applications is indelible, easy to read, difficult to copy or alter, contains unique serialization information, and does not change product functionality in any way (Heller, 2015).

Film coating is used in the pharmaceutical industry for solid dosage form because of visual attractiveness, trade marking issues, identifying, taste masking, improved product stability, shelf life increase or controlled release of the active pharmaceutical ingredient (API) (Koller et al., 2011; Korasa et al., 2016; Markl et al., 2014). Besides the above, colored coatings can also help to prevent counterfeiting. Since most of the tablets are round and white and, consequently, easier to fake, a unique and distinctive shape and color can improve identification and make counterfeiting more difficult (Pérez-Ibarbia et al., 2016).

Coloring and special shape are not enough to distinguish each tablet from one another. Further marking is necessary, especially for unique identification.

From among many different options, printing is one of the most attractive methods for marking as the capital equipment cost is relatively low. However, the printing process necessitates contact between the substrate and some form of ink carrier, toner reservoir, or stamp, so it could be a source of contamination. High printing speed is required for some of the fastest production lines and that can result in a loss of image quality and the risk of unreadable codes (Davison, 2011). Furthermore, the ink formulation has to be designed with respect to its viscosity and surface tension to guarantee continuous printing and high reproducibility of the forming droplets (Genina et al., 2012). In addition, chemical markers or colorants that are used on the surface of the dosage form must be materials that are tested and accepted as safe by the pharmaceutical authorities (Davison, 2011).

One of the other ways of marking could be done with infrared (IR) laser. It produces a surface mark through intense localized heating and it could cause damage in heat-sensitive materials (Gaebler, 2017).

Ultraviolet (UV) lasers overcome the drawbacks of the above-mentioned ink printing and IR laser printing technologies. UV laser marking is a non-contact method that avoids the problems of contamination and eliminates the cost of consumables. It undergoes a cold photochemical, rather than photothermal interaction. Since this is a cold process, there is essentially no Heat Affected Zone (HAZ) or changes to the surrounding material. Finally, since UV light can be more tightly focused than IR, UV lasers support complex, high-resolution marks such as 2D barcodes.

In the past UV lasers were rarely utilized because of their cost. However, over the past decade, companies reduced UV laser price by a factor of nearly five over this period (Heller, 2015).

The final aim of the present work is to develop a technology to mark an individual traceability code directly on the tablet. The plan is to make 2 layers of coatings on the surface. The first one is the functional one, and the other on the top of it would be applied because of the marking. The colors of the 2 coatings should contrast each other. By ablating the upper coating, we should be able to read the 2D data matrix code that will be formed of those two layers. The basic experiment for this article started with only one layer. We examined how the coated film behaves when it is treated with 3 different types of laser to be able to select the right instrument for further research. With excimer UV laser we made a square shape ablation for a start, which we plan to replace in the future with 2D code forming mask. With semiconductor laser we were able to mark a 2D barcode on the surface of the tablet. Unfortunately, the pulsed Nd:YAG laser damaged the coating film. By analytical quality tests, we were planning to select the right instrument for unique drug marking.

This investigation suggests the use of excimer UV laser for marking the tablet surface because this treatment minimizes the chemical degradation of the coating film during the process.

2. Materials and methods

2.1. Materials

2.1.1. Tablet core and coating materials

Tablet samples for laser marking preformulation were original tablets from the legal supply chain: Sinecod (GSK), Telfast (Sanofi), Klacid (Abbott), furthermore Eudraguard® control and HPMC coated placebo tablets.

In the further research round placebo tablets were used, with no break line (diameter: 7 mm, crown height: 4 mm). Aqueous-based enteric coating solution was prepared. It consisted of 52% w/w dry substance of a neutral copolymer based on ethyl acrylate and methyl methacrylate with a ratio of 2:1 (Eudraguard® control dispersion 30% w/w (Evonik Nutrition & Care GmbH)), 16% w/w talc, 28% w/w alginic acid sodium salt, 4% w/w glycerol, and distilled water. Coatings were colored with 1% w/w patent blau 85 (blue), 3% w/w Gelborange (orange), 1.5% w/w Azorubin (cherry) or 1.5% w/w Iron Oxide Red (red).