AlyPOTEC: Analysis of pharmaceutical counterfeits using terahertz technology

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Résumé – Le projet 'AlyPOTEC' a pour but d'améliorer la sécurité des citoyens vis-à-vis des contrefaçons, falsifications ou dégradations de la qualité des produits pharmaceutiques. Les applications envisagées pour ce projet sont typiquement : le contrôle douanier, le contrôle qualité ou l'authentification de produit par l'industrie pharmaceutique ou par des laboratoires de contrôle de médicaments officiels.

L'objectif de ce projet est de conduire une étude approfondie de ces produits. Les capacités de détection de la spectroscopie THz vis-à-vis des produits définis et des critères de contrefaçon seront évaluées. En effet, cette technique pourrait apporter une analyse complémentaire fournissant des informations supplémentaires sur le produit testé, son origine et son histoire (fabrication, composition, transport et stockage). Une analyse comparative avec des méthodes conventionnelles sera effectuée afin de mettre en évidence les atouts de la technique THz. Un prototype innovant, compact et mobile, basé sur des composants fibrés, sera développé en fonction des résultats de l'analyse des produits. Il sera ensuite validé sur des échantillons réels issus de saisies.

La multidisciplinarité revêt une importance particulière dans ce projet et est assurée par la complémentarité des compétences des partenaires : Institut franco-allemand de recherches de Saint-Louis (ISL), Université Paris Descartes (les laboratoires de Physico-Chimie Industrielle du Médicament et de Pharmacognosie), Horus Laser. De plus, deux représentants du secteur public de la sécurité et membres du comité de pilotage de ce projet : le Service Commun des Laboratoires (SCL) de la Douane et l'Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) apportent les informations essentielles sur les besoins opérationnels, principaux produits contrefaits et critères de détection.

Abstract – The project 'AlyPOTEC' aims to improve the citizen security with respect to counterfeit, falsified or poor quality pharmaceutical products. Targeted applications of the project are typically: customs controls, quality control or product authentication by pharmaceutical industrial, or by official medicine control laboratories.

The objective of the project is to carry out a comprehensive analysis of these products. A study of the detection capabilities of the THz spectroscopy towards selected samples and counterfeiting criteria will be performed. In fact, this technique could provide a complementary analysis, which will give further information on the counterfeit product origin and "history" (manufacturing process, composition, transport and storage). Comparative analysis with established methods will be achieved to highlight THz technology assets. An innovative, compact and mobile prototype will be developed using fiber coupled components according to the results of the product analysis. This system will be validated on real samples coming from seizures.

The project has a highly multidisciplinary character which is underlined by the complementarity of the competences of the partners: French-German Research Institute of Saint-Louis (ISL), two laboratories of the University Paris Descartes, and HORUS LASER. Furthermore, two representatives of the public security sector will provide crucial expertise: both the Service Commun des Laboratoires de la Douane and the Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) will give inputs on their operational needs, on the main counterfeited products, and on detection criteria.

1. Introduction

1.1 Context

The problematic of counterfeit, fake or poor quality products has been increasing over the last decades. In developed countries, this has mainly been the consequence of the access to Internet. In 2010, it was estimated that 50% of medicines purchased over Internet were counterfeited (falsely-labeled/falsified/counterfeit medicines). This very serious worldwide concern leads to the collaboration of various organizations (WHO), national and international institutions (customs, police, national regulatory health agencies, pharmaceutical manufacturers…) in order to constitute a network for the exchange of information, experience and technical expertise to control this situation such as the International Medicinal Products Anti-Counterfeiting Taskforce (IMPACT) created in 2006. In France, from 2001 and 2008, around 38 pharmacovigilance cases involving medicines bought over Internet were declared. They included 11 slimming products, 3 anabolic steroids and 8 stimulating hormone-based products (melatonin, DeHydroEpiAndrosterone, pregnenolone…). Since 2009, ANSM participates to the PANGEA operations on counterfeit and illegal medicines Internet sales (cybercrime) involving Interpol-PFIPC (Permanent Forum for International Pharmaceutical Crime), IMPACT and others stakeholders like World Customs Organization, Internet services (providers, payment systems). A very promising technology for detection and identification of these illicit substances is Terahertz (THz) spectroscopy. The THz region of the electromagnetic spectrum covers the frequency range between 300 GHz and 10 THz. THz radiation has a number of interesting properties that could lead to very innovative and novel applications. These properties include the ability to penetrate many non conducting materials, high spectral sensitivity and to be neither of hazardous nor of ionizing nature

1.2 Position of the projet

The potential of terahertz technologies for investigating pharmaceutical substances has recently been demonstrated. In particular, the fact that THz spectroscopy is very well suited to easily differentiate the polymorphic forms of a substance has significantly increased the interest of the pharmaceutical scientific community in this novel spectroscopic technique. Most of these pioneering studies have been performed in the UK, the US, and in Japan. Compared to the increasing research activities in this particular topic in these countries mentioned above, the corresponding research in France lags strongly behind. The THz research team at the ISL has over the past years acquired a pronounced expertise in the study of polymorphism and phase transitions. Another potential application of THz spectroscopy for investigating pharmaceutical substances has first been proposed by a UK based group: they exploit the pulsed nature of THz time-domain spectroscopy to determine the thickness of the individual layers. Thus, in addition to the analytical investigation of the active ingredients and excipients, THz spectroscopy allows to detect structural differences that could indicate a counterfeit.

While several THz spectroscopy and imaging projects have been subject of scientific studies over the past years, the application for the pharmaceutical domain has so far not been comprehensively investigated and thus did not receive substantial funding in France.

2. State of the art

2.1 Counterfeit medicines and current methods

Counterfeiting can apply to both branded and generic products. The counterfeit products may include drugs with the correct ingredients or with the wrong ingredients, without active ingredients or with insufficient active ingredient. The counterfeiting may also involve the packaging. Pharmaceutical counterfeits can be produced via several ways (e.g. change of the polymorphic form, change of at least one component, modification of the active principal ingredient(s)/excipient(s) ratio, different hydration state of the drug) [1][2]. The composition of the counterfeit product will be carefully determined by means of specially adapted techniques. Polymorphs have different stabilities and may spontaneously convert from a metastable form (unstable form) to the stable form at a particular temperature. They also exhibit different melting points, solubilities (which affect the dissolution rate of drug and consequently its bioavailability in the body) [3]. In addition, polymorphic forms show distinguishable X-ray crystal and diffraction patterns. As a matter of fact most drugs exhibit polymorphism. A conversion of the molecule from one polymorphic form to another occurs could lead in the worst case to a change of the bioavailability properties.

2.2 THz technology

According to [4] and [5] current analytical methods present some limitations and constraints. First reports on the potential of THz time domain spectroscopy (THz-TDS) for analytical studies of organic molecules have only been published a bit more than a decade ago [6] [7], which were authored and co-authored respectively by members of this consortium. Since then, an increased interest in THz technologies has led to an extremely fast development, and nowadays THz spectroscopy and imaging have reached a level of maturity which allows the transfer from a mainly laboratory based technique to various applications in many different fields [8]. Pioneering companies, which are mainly based in the US (Picometrix, Z-Omega), the UK (TeraView), and Germany (Menlo), offer different spectroscopy systems that are mainly optimized for detection purposes. None of these systems is developed or

manufactured in France. Similarly, imaging systems have recently become commercially available, again with a focus on German and US bases companies. There is a well-established strong French THz Scientific community, providing internationally recognized expertise in various domains ranging from THz imaging [9] [10], fundamental studies, hardware development [11] [12], gas spectroscopy [13], to detection applications for safety and security (eg. ANR/CSOSG 2011 Project InPoSec or [14]). Yet, the analytical potential of THz spectroscopy, in particular for pharmaceutical applications, has so far only been marginally exploited in France. This is in sharp contrast to the situation in other countries, mainly the UK and Japan, where the importance of the topic has been singled out earlier [15-18].

3. Presentation of the project

3.1 Objectives

THz technology has shown its high potential for applications in the security domain (detection of explosives, body scanning or postal inspection). The objective of the project AlyPOTEC is to demonstrate the ability of THz technology to be applied to the security of pharmaceutical chain and more particularly to the detection, identification and characterization of counterfeit, falsified or poor quality medicines. This project is the first in France combining scientific groups, security end-user as well as an official medicines control laboratory. The academic partners will provide knowledge on the chemical and physical-chemical aspects of the tested products. Referring to the strong expertise of the consortium and steering committee (SC), it will be possible to study THz signatures of medicines with a time domain spectroscopy (THz-TDS) system. ISL and Horus Laser will develop an innovative and apposite THz sensor.

A first technical objective of this project is to define the most counterfeited medicines and the associated types of counterfeit (in term of composition) using the experience of the SC. A second objective is to determine the THz ability to detect pharmaceutical ingredients: active ingredient and excipients as well as potential contaminants. A detailed study of the detection capacities: concentration threshold, mixture effects is foreseen. Then the performances of the proposed technology with respect to quasi similar products (polymorphs, isomers and anomers) will be addressed. Once again the academic partners will provide expertise in this domain. Another goal is to compare THz spectra with traditional methods in order to highlight THz time domain spectroscopy assets. A prototype of a THz time domain spectroscopy system will be designed and manufactured. It will fit the specifics of the SCL and ANSM.

It has been shown over the last decade that THz technology is a good candidate for multiple applications and especially for the security sector. Nevertheless, it has suffered for a long time of a lack of compact, reliable and reasonable cost sources or detectors. Maturity was not sufficient to allow for industrial or mass market applications. The use of fiber coupled laser and components working at telecommunication wavelength (1550 nm) should enable to improve the above mentioned features. Nevertheless, using optic fibers can induce degradations on the laser pulse (dispersion, non linear effects, etc.) necessary for the generation and detection of the THz radiation. Therefore the expertise of Horus Laser will be of outmost importance to overcome these drawbacks. Another point is the specifics related to the domain of pharmaceutical control. In fact there are some constraints in term of eg. normalization and conformance with EU regulation. The aspects should be addressed thanks to the academic partners and ANSM.

A report will summarize the results and conclusion of the product analysis with THz-TDS (including comparisons with traditional methods). It should be demonstrated that THz can be a complementary but more convenient (in term of speed, compactness, ease of sample preparation or operating conditions) tool for such an application.

As far as the prototype is concerned, an innovative system will be provided. It will be based upon fiber coupled components, emitter and detector photocommutators, in order to optimize compactness, reliability and mobility. This choice will also ensure controlled costs. A dedicated software will achieve data acquisition, post-processing and visualization of the results. It will include a user friendly interface.

3.2 Scientific program

The scientific program of this project is composed of one task for the management, one task dedicated to communication and dissemination and five technical tasks as shown on the following schematic Fig.1.

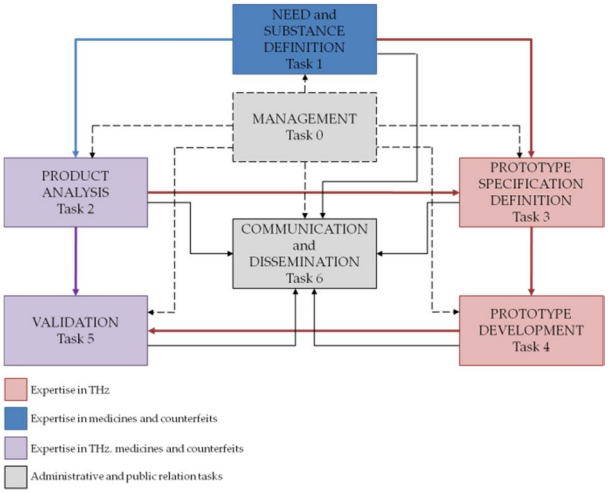

FIG. 1: Schematic of the tasks

As this project is multidisciplinary, tasks have been divided in such a way that it favours exchanges and interdisciplinarity but also lowering risks.

In the first strategic task (1) potential types of counterfeits to be analysed by the proposed sensor system will be considered and discussed. For this purpose, the consortium coordinator will be in very close contact with the end user SCL, the pharmaceutical security expert ANSM of the steering committee. The discussion should end by the definition of the main types of counterfeits (in term of composition) which circulate and on the main medicines that are counterfeited. The aim is to obtain a specification sheet including a (first) concrete list of substances to be investigated. The background of the participants will ensure that the counterfeit specificities as well as the nature of potential threats are properly considered.

In the next task (2), the main part of the fundamental aspects of this project will be carried out, namely the analysis of the products. These investigations will be performed with conventional methods associated with a comprehensive study of the THz spectra. This will focus on active pharmaceutical ingredients (API), excipients, and contaminants. Different parameters will be studied such as concentration detection thresholds, molecular structural configurations, and through-packaging measurement capabilities, etc.

The two next tasks (3) and (4) concern hardware aspects: first defining the specifications of the prototype given the first results of the previous task and end user needs; and then prototype development. In order to reach optimum compactness, transportability, reliability (robustness with respect to vibrations, dust or external conditions), fiber coupled components will be implemented. The prototype will include a user interface which will (i) control the data acquisition, (ii) perform post-processing and (iii) enable visualization of the sample images and spectra.

A validation phase will finally be on real products coming from seizures provided by steering committee partners. Comparisons with traditional analytical methods will be achieved to emphasis the advantages of the proposed technique.

The sixth task dealing with communication and dissemination is transversal: it involves all the partners and will last the duration of the project. In order to inform the general public about the global context, advances, and news and events of this project, a dedicated internet website will be developed.

4. Conclusion and future work

The project AlyPOTEC aims for providing a new innovative and complementary tool which should enable to have a better knowledge of the counterfeit medicines.

The project has just very recently started. This first year will be dedicated to the selection of the counterfeit medicines and substances to be studied in the frame of the project. Based on the expertise of the end users, a list will be established which will include key information about these products. At the end of the first year of the project, the second task will start, which consists of the analysis of the products via both traditional and THz technologies.

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