International Journal of Pharmaceutics 532 (2017) 299–312

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Review

Emerging technologies for the non-invasive characterization of physical-mechanical properties of tablets

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ARTICLE INFO

Keywords:
Tablet physical-mechanical properties
Density
Porosity
Tablet breaking force
Pharmacopeial methods
Emerging technologies

ABSTRACT

The density, porosity, breaking force, viscoelastic properties, and the presence or absence of any structural defects or irregularities are important physical-mechanical quality attributes of popular solid dosage forms like tablets. The irregularities associated with these attributes may influence the drug product functionality. Thus, an accurate and efficient characterization of these properties is critical for successful development and manufacturing of a robust tablets. These properties are mainly analyzed and monitored with traditional pharmacopeial and non-pharmacopeial methods. Such methods are associated with several challenges such as lack of spatial resolution, efficiency, or sample-sparing attributes.

Recent advances in technology, design, instrumentation, and software have led to the emergence of newer techniques for non-invasive characterization of physical-mechanical properties of tablets. These techniques include near infrared spectroscopy, Raman spectroscopy, X-ray microtomography, nuclear magnetic resonance (NMR) imaging, terahertz pulsed imaging, laser-induced breakdown spectroscopy, and various acoustic- and thermal-based techniques. Such state-of-the-art techniques are currently applied at various stages of development and manufacturing of tablets at industrial scale. Each technique has specific advantages or challenges with respect to operational efficiency and cost, compared to traditional analytical methods. Currently, most of these techniques are used as secondary analytical tools to support the traditional methods in characterizing or monitoring tablet quality attributes. Therefore, further development in the instrumentation and software, and studies on the applications are necessary for their adoption in routine analysis and monitoring of tablet physical-mechanical properties.

1. Introduction

Pharmaceutical tablets are composed of one or more active pharmaceutical ingredients (API) and non-active ingredients. They are the most common form of oral drug administration. Tablet manufacturing is a complex process consisting of several unit operations. A key expectation of tablets with acceptable quality and functionality is the retention of its strength during handling, and maintaining dosage-form integrity until administration. Moreover, it must undergo disintegration, dissolution, and release of the drug efficiently upon administration. The delivery of drugs from a tablet is greatly influenced by its composition and physical-mechanical properties such as geometric dimensions, density, breaking force etc. (Stephens et al., 2013b). Ideally, tablets should also be free from any structural defects or irregularities. Consequently, it is imperative to measure tablet physical-mechanical properties with highly accurate and precise techniques, which allows a timely characterization and monitoring of tablet properties such as porosity, elasticity, and breaking force. The tablet formulation composition and the manufacturing process are often known to cause structural defects such as capping, chipping, cracking, sticking, and lamination. These defects and are considered among important developmental challenges in the industry (Cetinkaya et al., 2010). Structural and functional failures in tablets often result in delayed regulatory approval, delayed time to market or in case of post-approval failures, product recalls from the market. Eventually these failures add economic burdens on the overall cost of the final product.

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http://dx.doi.org/10.1016/j.ijpharm.2017.09.009
Received 16 April 2017; Received in revised form 31 August 2017; Accepted 4 September 2017
Available online 06 September 2017
0378-5173/

Pharmacopeias typically provide guidelines and standards to evaluate tablet properties such as homogeneity, friability, content uniformity, breaking force, disintegration, and dissolution. According to the '*Q6A specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*' The USFDA requires the use of these pharmacopeial guideline and standards for drug products. A majority of pharmacopeial techniques is semi-destructive to the samples. Often these tests lack specificity and spatial resolution. Furthermore, specific tests may vary significantly across different pharmacopeias due to applied testing parameters (Donauer and Löbenberg, 2007). Moreover, according to the Q6A specifications, the USFDA encourages the use of any new analytical technologies when they are considered to offer additional assurance of quality, or are otherwise justified. The past few decades have witnessed the development of several efficient, sensitive, practical, material-sparing, and non-invasive techniques for the evaluation of tablet properties (Fevotte et al., 2014). These techniques include, near infrared spectroscopy, Raman spectroscopy, x-ray microtomography, nuclear magnetic resonance imaging, terahertz pulsed imaging, laser-induced breakdown spectroscopy, acoustic and thermal techniques.

While a comprehensive analysis of all the techniques is beyond the purview of this article, the present review sheds light on the commonly existing methods and elaborates on the emergence of non-invasive analytical tools used for the characterization of physical-mechanical properties pharmaceutical tablets. The following sections, in no specific order, describe the most explored, and some newer technologies. The discussion of individual technology is mainly focused on the operation principle, applications, advantages, and limitations of the technique.

2. Current pharmacopeial/non-pharmacopeial methods

Pharmacopeial conventions establish standards that must be followed by all marketed drug products to ensure their quality, strength, identity, and permissible impurity limits. The United States Pharmacopeia (USP) provides guidelines and standards to assess several properties of pharmaceutical tablets, such as homogeneity, friability, content uniformity, breaking force, disintegration, and dissolution (Zeitler and Gladden, 2009).

The measured porosity is described as the proportion of empty space, or pores, in a compressed tablet, and reflects the solid fraction of a tablet (Wikberg and Alderborn, 1990; Yuasa et al., 1996). The porosity of a compact is determined by two methods described in the USP (Porosimetry by Mercury Intrusion, and by Nitrogen Adsorption-Desorption). In order to obtain meaningful results, it is imperative to standardize the displacement medium, since the porosity measurements can vary significantly with the medium. The friability test, as described in the USP determines the ability of pharmaceutical tablets to tolerate stresses during manufacturing, packaging, and transportation. The test involves subjecting the tablets to a uniform tumbling motion in a drum (friabilator) for a specified period/number of rotations, and measuring the percent weight loss. The externally applied force, which results in the breaking of a tablet in a specific plane is commonly used to analyze the mechanical integrity of tablets (Brook and Marshall, 1968). The USP Chapter on tablet breaking force provides guidelines to analyze the breaking force of tablets. Diametrical hardness testing of tablets is routinely carried out during manufacturing as a part of in-process quality monitoring and control (Fell and Newton, 1970). The evaluation is typically conducted by placing a tablet perpendicular to its banded side (round tablets) or along the longest length (oval tablets) on a platform. The tablet is then crushed with a flat-faced cylindrical probe moving at a constant, set speed. (Brook and Marshall, 1968). Several variants of tablet hardness testers ranging from manual to automatic are currently being utilized (Bavitz et al., 1973; Fairchild and Michel, 1961; Goodhart et al., 1973; McCallum et al., 1955).

In addition to the traditional quality control tests for tablets, coated tablets are evaluated for the characteristics of the coating films. These evaluations include, (i) adhesion test using a tensile strength tester that determines the force required to remove the coating film from the tablet surface, (ii) evaluation of coating film strength by determining the difference in the breaking force of the coated tablet relative to the uncoated tablet, (iii) effects of temperature and humidity on the film integrity, and (iv) qualitative and quantitative determination of surface roughness, hardness, color homogeneity, etc. of the film, which could be inspected visually or by specific instruments (Zeitler and Gladden, 2009). In addition, coated tablets are tested for film resilience empirically by rubbing the tablets on a white paper sheet, and visual observation of film integrity as well as any transfer of film color on the paper.

Along with the pharmacopeial tests, several non-pharmacopeial techniques are also routinely employed as a secondary supportive measures of the physical-mechanical properties of tablets. The most common among these include the Hiestand Tableting Indices (Hiestand et al., 1971; Hiestand, 1996; Hiestand and Smith, 1984). For materials previously characterized for their physical-mechanical properties, these indices indicate their relative tableting and consolidation behavior. The degree of particle bonding within a tablet that remains after decompression, measured as a ratio of tablet tensile strength and breaking force is known as the *bonding index*. The brittleness of the material, obtained by comparing the tablet tensile strength and the indentation hardness, is indicated by the *brittle fracture index*. The brittle fracture index assists in predicting the probability of capping and lamination. The viscoelastic properties of tableting materials is obtained from the ratio of dynamic indentation harness and the quasi-static tablet breaking force, and known as the *viscoelastic index*.

Most of the pharmacopeial and non-pharmacopeial techniques described above are semi-destructive or invasive to the samples. Moreover, some of these tests lack specificity and spatial resolution. Furthermore, specific tests vary considerably across different pharmacopeias (Donauer and Löbenberg, 2007). Nevertheless, these techniques are useful, have been used for many years, and have significantly contributed to the development of pharmaceutical tablet products.

3. Emerging technologies

3.1. Near infrared spectroscopy

Near infrared spectroscopy (NIRS) is among the most commonly used analytical tools in pharmaceutical development. Since the early 1990s, several studies and review articles have shed light on various applications of NIRS (Aldridge et al., 1994; Morisseau and Rhodes, 1995, 1997). NIR is defined as the section of the electromagnetic spectrum between 780 and 2526 nm. In this spectral area, the fundamental vibrations of specific functional groups (e.g. −CH, −NH, −OH, SH, etc.) on the molecules interact with radiation to produce specific spectral bands. These NIR bands are also highly sensitive and responds to the physical and chemical characteristics of the analyte. These properties make NIRS a useful tool for the analytical investigation of samples with high absorption and/or scattering properties e.g. solids. Typically, NIR analyzers are generally consist of a radiation source, a radiation processing unit, a sample presentation unit, and signal acquisition/processing unit (Fig. 1).

The NIR spectra, however, are broad and consist of overlapping and fused peaks. Thus, in order to extract meaningful information, NIR spectra require systematic data processing with the use of Chemometrics (Dave et al., 2015, 2017). Moreover, development of robust multivariate calibration models using large datasets, and validation of the developed models is required to reliably use NIRS for the qualitative and quantitative examination of materials. NIRS, along with Chemometrics-assisted model development, have resulted in its extensive applications in research, production, product quality assessment, and control of pharmaceutical products (Dave et al., 2015; Uppaluri et al., 2014). A wide variety of NIRS measurement