Hardness Testing of Pharmaceutical Tablets

A technical primer for attorneys

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1. Introduction: What is harness testing?

Hardness testing is a simple methodology to interrogate one of the key properties of tablets: the tensile strength. Tensile strength is the value of the stretching force divided by the area perpendicular to that force at the breaking point or fracture of the material. Units for this quantity are force per unit area which are usually expressed in the metric system in Newton per square millimeter (N/mm^2) or in the U.S. Customary System in pounds per square inch (lb/in^2). Tensile strength is the most critical, representative and commonly used parameter used in material sciences to characterize, classify and identify materials. There are many different experimental settings to measure this property including several standards for different type of materials, conditions and environments. For testing this property in pharmaceutical tablets, the US Pharmacopeia provide in chapter <1217> Tablet Breaking Force, two different methodologies, a) diametral compression and b) 3-point bending. Since the most common methodology used in the pharmaceutical industry is diametral compression which is commonly named HARDNESS in the pharmaceutical community, we limit our discussion to this case.

First, what is the diametral compression test? It is a procedure to simply measure the value of the compressive force or breaking force (F) applied along the diameter of a disk at failure. The value of this breaking force is proportional to the tensile strength (σ) of the material, more specifically $\sigma = F/A$, with $A = \pi R t$ where R and t are the radius and thickness of the disk respectively. It should be emphasized the simplicity of this test for measuring the tensile strength (σ) of disks by applying a compressive load (F) that avoiding the fabrication of samples for direct tension or bending as well as deploying intricate gripping conditions. In addition, thanks to solid mechanics, the relation between σ and F is simple, clean and precise. In fact, Mechanics (see for example: S. P. TIMOSHENKO and J. N. GOODIER, "Theory of elasticity" McGraw-Hill, New York, 1970) teaches us that the splitting (tensile) stress across the diametral line is **uniform** for a disk of radius R and thickness t made out of an infinitely stiff material. This theoretical result is the centerpiece for the adoption of this test configuration for measuring tensile stress. It is instructive to keep these principles in mind for assessing its applicability, validity as well as recognizing potential pitfalls and limitations.

2. Hardness in pharmaceutical patent litigation

Hardness is commonly used in patents involving pharmaceutical products in the form of tablets in order to describe some of the characteristics of the invention. In fact, different aspects of pharmaceutical litigation can use tensile strength (hardness) test results:

- Literal Infringement: When the patent claims contain explicit language regarding hardness tests performed on an accused product can support arguments of literal infringement.

- DOE Infringement: even when explicit language is not present in the claim, hardness results can be used to support arguments that two formulations, or two manufacturing processes, are "equivalent", because they are producing "the same result".

- Invalidity due to anticipation or obviousness: If the claim contains explicit language about hardness defining the "product of the invention", hardness results can demonstrate that prior art formulations were already achieving, or could be expected to achieve, the "inventive" result.

- Invalidity due to indefiniteness: the values of the hardness tests performed on tablets with non-circular shapes depend on the orientation of the tablet respect to the load. Patents without specifying the testing configuration can give rise to strong indefiniteness (or lack of written description) arguments.

3. Hardness in other types of pharmaceutical litigation

In addition to patent litigation, mechanical strength can be important to a number of other types of litigation. For example, for abuse deterrent formulations a product that fails to achieve minimum requirements for a tamper resistance might lead to potential serious liabilities.

4. Analyzing hardness test results

The hardness of pharmaceutical products carries significant information about the characteristics of ingredients and processing conditions during manufacturing, which may be critical in discriminating pharmaceutical products. Most of pharmaceutical tablets are made by compaction of powder blends using a rotary tablet press. For a given blend, the hardness strongly dependent on tablet porosity after the compaction process. This porosity is inversely proportional to the maximum applied force. As seen in Figure 1, the hardness-porosity relation is highly nonlinear and it is well described by an exponential law.

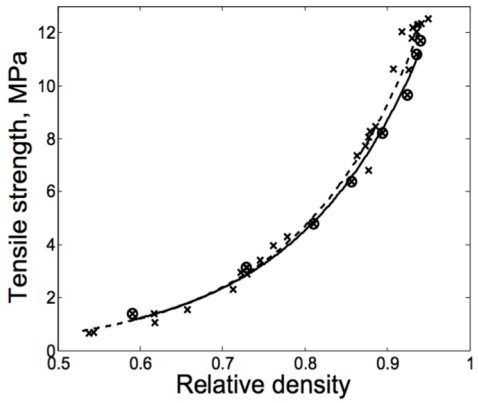

Figure 1. Typical Tensile strength vs Relative density. Note that Porosity = 1 - Relative density. For example, 2% Porosity corresponds to 98% Relative density. Tensile strength or hardness is measured by diametrical compression, (from IJP 484, 29-37).

For example, studying the hardness data for a given formulation, it is possible to extract the differences in the degree of lubrication as well as the amount of lubricant present in the powder blend, and thus, proving information about history of the mixing process utilized as well as the details of the composition. Similarly, analysis of hardness data can provide information about other process parameters and components such wet and dry granulation conditions, particle size distribution, type of equipment, speed of compaction and pre-compaction forces among others.

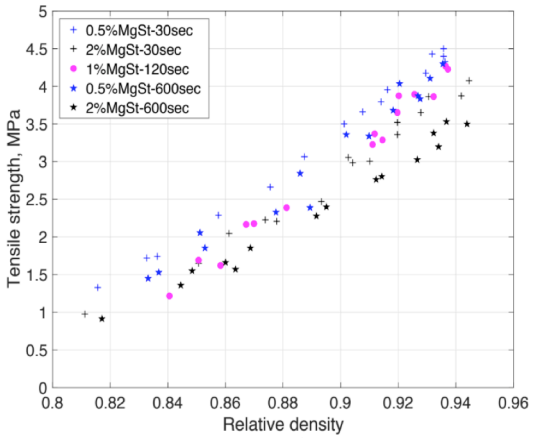

Figure 2. Tensile strength vs Relative density for a formulation with different amount of Magnesium Stearate (lubricant) and different mount of mixing in seconds. (from Powder Technology, 336, 360-37)

5. Common pitfalls in performing the hardness

Despite the simplicity of the test, there are some of issues to keep an eye on:

- *Tablet Shape.* The relation simple between the applied force and tablet strength is only intended for cylindrical shapes (disks). For other shapes, there is a number of approximating formulas rendering different degree of accuracy. For tablets that are close to disks, these approximations are generally acceptable, but for other shapes may not be the case, especially those that the mode of failure is no longer across the diameter.
- *Tablet Orientation* for tablets with a non-circular shape like ellipsoidal, triangular, etc. In those cases, it is important to indicate the direction of the load relative to the tablet. Loads can significantly change according to the orientation used.
- *Ductile Materials.* The diametral compression test is only intended for materials that break with relatively small deformation. For ductile materials (those exhibiting large deformation before failure), such as, for example, most opioid products, the stress distribution is significantly altered and the hardness formulate no longer provides a good approximation for determining the tensile strength.

6. Resources Available at Acumen Biopharma

Acumen Biopharma has extensive experience regarding the role of hardness testing in formulation, quality control, and litigation. We can assist attorneys in understanding the role of dissolution test results in a given case, both for background purposes or for litigation. Acumen Biopharma maintains service agreements with multiple academic and industrial laboratories to enable us to specify and perform hardness tests as well as other mechanical tests quickly and reliably, including DEA licensed labs that can handle controlled substances. We have developed protocols to support the selection of the proper test for a given purpose.

Moreover, since Acumen Biopharma has assisted many law firms in analyzing and performing test results, our protocols include effective methods for ensuring data quality and integrity, including chain of custody protocols, equipment and method calibration, and extensive documentation practices that include electronic record keeping, laboratory notebooks, photographs and videos.

We are always happy to discuss technical issues. Many more details are available upon request. For more information, please contact us.

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