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Mechanical strength test for orodispersible and buccal films

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ABSTRACT

There are no test procedures, definitions and specifications available how to determine mechanical strength of orodispersible or buccal films. Aim of the study was to develop an appropriate and discriminating method to feature the evaluation of marketed and newly developed film products covering well-known and new approaches. The limits for mechanical strength were set starting from a puncture strength of 0.06 N/mm^2 according to the obtained results from marketed products. Furthermore, elongation to break of the marketed films (1.03–6.54%) and prepared film samples (4.51–33.17%) offered information on the film properties. The developed mechanical strength test method was suitable for all film types without the need of a pre-defined specimen. A mechanical strength threshold could be specified for future orodispersible film development.

1. Introduction

Orodispersible films (ODFs) are a new type of dosage form that is intended to dissolve rapidly in the oral cavity. They became popular in terms of chewing gum alternatives for mouth refreshing, but most recently they gained interest in pharmaceutical sciences and industry because of their ability to administer active pharmaceutical ingredients (API) alternatively to common tablets and orodispersible tablets (Hoffmann et al., 2011). Film preparations may be produced by solvent casting, which is the most common way of manufacturing. Film forming agents (e.g. hydrophilic polymers) are dissolved in a solvent and resulting solutions is poured onto a flat surface. After the solvent evaporated, a thin polymer film remains that can be further processed (e.g. cutting, packaging) (Preis et al., 2013).

ODFs have become part of the "oromucosal preparations" monograph of the European Pharmacopoeia (Ph.Eur. 7.4) most recently (EDQM, 2012a). Mucoadhesive buccal films (MBFs) were included in the subchapter "mucoadhesive preparations". The elaboration of details is limited due to novelty of the monograph. Upon other terms, the following is required according to the Pharmacopoeia: "In the manufacture of orodispersible films, measures are taken to ensure that they possess suitable mechanical strength to resist handling without being damaged". Unfortunately, no detailed description is provided to evaluate the mentioned mechanical strength. Therefore, standardized test methods and related specification limits are needed to characterize this innovative dosage form.

As far as tablets are concerned, methods to evaluate mechanical strength are provided by the Ph.Eur. (EDQM, 2012b). However, these methods aiming at the breaking strength and cannot be transferred for ODFs.

Both ODFs and MBFs are thin sheets mostly prepared from hydrophilic polymers. Detailed information on manufacturing process (Hoffmann et al., 2011) and present studies on film characterization has been provided elsewhere (Preis et al., 2013). Briefly, ODFs and MBFs are prepared by dispersing a film forming polymer in a solvent. The solution is subsequently cast on a flat surface (solvent casting method). These films may also be manufactured by laminar hot-melt extrusion (Repka et al., 2003). The main difference between ODFs and MBFs is the fact that ODFs should disperse rapidly when placed in the mouth, an MBF may maintain in the oral cavity permanently (and needs to be removed) or disperse slowly, e.g. for prolonged drug delivery.

The mechanical strength of film formulations is a crucial factor not only during the production or development, but also regarding the proper handling by the patient. There are different factors influencing the mechanical properties of films: film forming agent, type and amount of plasticizer, type and amount of (residual) solvents, thickness of the final film sheets, type of manufacturing process, storage conditions and the type and amount of API in the film. Depending on drug properties and additives, the substances will

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be homogeneously dispersed in the film or suspended (Preis et al., 2012). The morphological state of the film may impact the mechanical strength, e.g. by crystal growth. Therefore, these aspects have to be considered during the development of films for pharmaceutical use. Mechanical strength is an important requirement to ensure damage-free production, packaging and when the product is released to the market: handling by the patient.

The amount of residual solvents and plasticizing agents, for example, may significantly influence film flexibility and ability to elongate. A certain elasticity is desired to avoid brittleness, which would make it impossible to wound the films up on large rolls during production. Films that are too flexible would cause problems as well: elongation during cutting and packaging might lead to deviations in film amount resulting in variation of the API amount per film.

Manufactures have to make sure that the mechanical properties of their product remain almost the same after being handed to the patient. As humidity and moisture content, respectively, were already mentioned as crucial factors for stability, temperature during storage plays an important role as well. An in-use-stability has to be ensured. This aspect reveals the importance of characterization methods to determine mechanical strength of film formulations at any stage of development.

Literature reveals several approaches to determine mechanical strength (also called tensile or breaking strength). The use of a standardized tensile test method by the DIN EN ISO 527 for foil materials was transferred for film purposes (Garsuch and Breitkreutz, 2009; DIN, 1996, 2003). Disadvantage of this approach is the low sensitivity of the apparatus due to its main purpose for industrial tough and robust materials and the need of using a described bone shape specimen of 80 mm length (DIN, 2003), which does not match the common sizes and geometry of an ODF. Most ODFs have a rectangular geometry and are sized between 2 and 8 cm^2 (Garsuch, 2009). Therefore, no reference samples such as marketed film products could be taken into account for comparison purposes. Systems like the Texture Analyser were used before to perform mechanical strength determination using ODFs, but films were required to be cut into a dumbbell standard template, similar to the aforementioned standard specimen (Boateng et al., 2009).

In 1988 Radebaugh et al. published a promising approach describing a puncture test system for pharmaceutical polymeric films (Radebaugh et al., 1988). Unfortunately, only few samples were investigated and there was no reference sample offering the opportunity to transfer or evaluate the results in terms of mechanical strength and practical applicability. A similar approach was described by Bodmeier and Paeratakul using a comparable setup to investigate dry and wet strengths of polymer films for solid dosage form coatings (Bodmeier and Paeratakul, 1993). Both approaches used a hemispherical probe to determine the puncture strength. As it could not be defined how this hemisphere penetrated into the sample, the area used for strength calculation was estimated as the cross sectional area located in the path of the cylindrical opening. The use of a cylindrical probe with a plane flat-faced surface might be advantageous, as the area directly affected by the strain is defined.

The basic principle of the reported puncture tests was used to develop the mechanical strength test method described in the present paper. However the proposed setup needed modification for adaption to ODFs and MBFs. Aim of this study was to develop a test system meeting the following requirements and properties:

- basic test setup, simple to adopt;
- feasible for both marketed film products and film formulations under development;
- applicability on small sized film pieces;
- determination of a clear endpoint of mechanical strength;
- predictability for required properties for performance in industrial manufacturing.

To accomplish the setup and further refinements, three groups of test specimen were investigated. Reference samples were chosen to pre-validate the novel mechanical strength test system. Subsequently, marketed film products were randomly selected to run the experimental setup. Following the evaluation of marketed products, newly developed ODF formulations were tested and results were assessed according to the findings in reference and market sample evaluation.

2. Materials

Eight marketed products with orodispersible films technology were investigated: eclipseFLASH™ (Wrigley, Unterhaching, Germany), Gas-X THIN STRIPS® (Novartis Consumer Health, Parsippany, USA), Listerine® Breath Strips (Johnson & Johnson, Skillman, USA), Pedia-Lax™ Quick Dissolve Strip (C.B. Fleet, Lynchburg, USA), Risperidon HEXAL® SF (Hexal, Holzkirchen, Germany), Smartstrips™ (Velox, Weston, USA), Triaminic Thin Strips® Cold and Triaminic Thin Strips® Cold & Cough (Novartis Consumer Health, Parsippany, USA). Table 1 displays the labeled ingredients of the marketed products.

Orodispersible film samples were prepared using the following film formers: polyacrylic acid (Carbopol Ultrez 10NF, Lubrizol, Wickliffe, USA), hydroxypropyl cellulose (Klucel JXF, Ashland, Wilmington, USA), polyethylene glycol–polyvinylalcohol co-polymer (PPACP, Kollicoat®Protect, BASF, Ludwigshafen, Germany), hypromellose (Pharmacoat®606, Syntapharm, Mülheim, Germany), methyl cellulose (Methocel A4C Premium (Colorcon, Dartford, UK), hydroxyethyl cellulose (Natrosol 250 G, Ashland, Wilmington, USA). Anhydrous glycerin (Caesar & Loretz, Hilden, Germany) was used as plasticizer. Filling material microcrystalline cellulose was obtained from Sanaq (MCC Sanaq 101, Basel, Switzerland) and crospovidone (PVPP) Kollidon CL-M from BASF (Ludwigshafen, Germany). Used solvents (water, ethanol) were of analytical grade. An overview on film composition is given in Table 2.

Common white paper sheets (HIG office supply, Karlsfeld, Germany), soft tissue (tissue – extra soft, Tork, Göteborg, Sweden) made out of virgin pulp fibers (cellulosic material) (Tork, 2013) and polyethylene terephthalate (PET) foil used for bottle pack wrappings (CocaCola, Essen, Germany) were used as reference material during method development. These three reference materials were chosen according to their differences in mechanical behavior. Paper, as it is commonly used, is a stable material that does not visibly elongate e.g. under manual strain. The soft tissue material is used e.g. as facial tissue, it is a thin and smooth material, stable enough to resist handling, but more flexible than a paper sheet. The PET foil is a material, which can be described as very flexible and stretchable. Therefore, it was chosen as third material to complement the references to cover three different types of material.

3. Methods

3.1. Film preparation

Film samples were prepared by solvent casting (Garsuch and Breitkreutz, 2009; Hoffmann et al., 2011). Film former, filling material and plasticizer were mixed in the solvent and allowed to homogenize overnight using a magnetic stirrer. The film solution was subsequently poured onto a film casting apparatus (Erichsen