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In vitro techniques to evaluate buccal films

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ABSTRACT

Extensive research on transmucosal drug delivery in the past few decades has resulted in the clinical application of several drug molecules through the buccal route. Interestingly, most of the new chemical moieties under clinical trials are being screened for their potential to deliver through the buccal cavity. In this context, buccal film offers several advantages including convenient dosing and better patient compliance. However, the greatest challenge is to develop a high quality buccal film which also necessitates constant evaluation and understanding the performance of the dosage form, the critical steps to achieve a successful product development. Despite the intense focus on buccal film based drug delivery system, there are no official standardized methods for its evaluation. Significant efforts have been made to demonstrate and improve the efficacy, potency and safety of buccal film using *in vitro*, *ex vivo* and *in vivo* assessments. Besides the physical properties of the film, several other parameters such as residence time, mucoadhesion, drug release, *in vitro* and *in vivo* buccal permeation profiles and absorption kinetics of the drug are examined while characterizing the prepared buccal films. However, various research groups have employed different methods and experimental conditions to evaluate the formulation, which has limited the comparison of data between the research groups. This review provides an overview about the various parameters that are considered and assessed as a part of formulation development to ensure quality product with desired characteristics.

1. Introduction

Formulation as well as evaluation of oral dosage forms may be quite challenging with newer and innovative dimensions being increasingly added to pharmaceutical products. Among the oral drug delivery route, the mucus membrane of the mouth has been identified as a potential site for the absorption of drugs. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for drug delivery and has received considerable attention in the last decade [1,2]. Compared to nasal drug delivery, the buccal route has been extensively studied as a site of drug delivery and has been elaborated elsewhere [3–5]. This route promises to deliver the drug molecules rapidly when demanding immediate effect, but could be used for control delivery as well [6]. Buccal dosage forms are designed for both local and systemic effects and the buccal drug delivery is currently considered as a primary route for drugs which suffer from first pass effect. Formulations such as tablets, lozenges, chewing gums, sprays, films, patches, hydrogels, paste, ointments, solutions, microspheres *etc*. are developed for the delivery through the buccal mucosa. Among these, the buccal film is reported to be the most promising and successful approach for the effective delivery through the epithelium and possesses higher patient compliance [7].

Typically, buccal films are postage stamp sized thin layer, fabricated using mucoadhesive and film forming polymers, loaded with the active pharmaceutical ingredient(s) [8]. The greatest advantage being that they do not require the formulation to be swallowed and can be applied even to a comatose patient. Conversely, the buccal films are more suitable than tablets owing to their better adaptation to the mucosal surface. Moreover, they provide long residence time and effective treatment in local infections wherein they protect the wound and reduce the pain [7]. Further, the advances in technology and biomaterials provide an upper hand for the scientists to meet the challenges and fabricate a film based drug delivery system pertinent to the buccal cavity. This dosage form is not official in Pharmacopoeias, although the pharmaceutical industry has recognized them as a potential means of delivering the active pharmaceutical ingredients. Moreover, this dosage form has reached commercial status with fentanyl as a transmucosal buccal device (Onsolis®) was launched in the market and many more candidates

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such as benzodiazepines, buprenorphine, morphine, captopril *etc.* are under clinical trials [1,5]. The ideal buccal film should exhibit adequate flexibility, elasticity, softness, resist the breakage due to stress from oral activities, good mucoadhesive strength, endure the movement of buccal cavity *etc.* All these parameters need to be evaluated during the formulation development stage and required standard protocols. Several techniques can be applied to characterize and evaluate the buccal films and are based on methods ranging from the physical properties through buccoadhesive, *in vitro* permeation to *in vivo* absorption in humans. This review outlines various *in vitro* and *in vivo* methods which are utilized in the pharmaceutical industries, regulatory agencies and drug delivery scientists to characterize the physical properties, bioadhesive nature, permeability, absorption *etc.* of a buccal film.

2. Physical properties

The evaluation protocols for buccal films are much similar to the other pharmaceutical films such as transdermal films. Routine test such as thickness, weight variation, film endurance, flexibility, water absorption, surface morphology, moisture content *etc.* are been evaluated for the prepared films. The determination of the mechanical properties of a buccal film is usually based on the ASTM D882-01 method [9]. It is generally assessed by the tensile strength, Young's modulus, percent elongations, tear resistance, porosity *etc.*, which provide the strength, robustness and ductility of the dosage form. In addition, the prepared films are characterized by scanning electron microscopy (SEM), X-ray diffraction, differential scanning calorimeter, Fourier transform infrared spectroscopy (FTIR) *etc.* In general, the mechanical properties of the film vary significantly depending on the polymer and to a certain extent on the method by which it is fabricated. For instance, the soft and weak polymers possess low tensile strength, Young's modulus and elongation at break. The following sections describe the various physical properties which are generally evaluated for the buccal films and the formulation composition which is likely to influence them.

2.1. Thickness and weight variations

The thickness of the films is usually measured using well calibrated electronic digital micrometer, screw gauge, vernier caliper or by SEM images. Indeed, the measurement of thickness of the film is essential to ascertain the uniformity of the film thickness as it is directly related to the accuracy of dose in the film. Moreover, an optimum thickness is necessary to provide adequate bioadhesion. Further, the choice of polymer is critical as certain polymers (polyvinylpyrrolidone, eudragit *etc.*) are known to increase the thickness of the film [10,11]. Furthermore, the incorporation of plasticizer into the formulation may also influence the film thickness [12,13]. In general, an ideal buccal film should exhibit a thickness between 50 and 1000 μm.

For weight variation, individual patches are weighed and the average weights are calculated. Then the average weight of the patches is subtracted from the individual weight of the patches. A large variation in weight indicates the inefficiency of the method employed and is likely to have non-uniform drug content.

2.2. Tensile strength

The mechanical properties play a crucial role on the physical integrity of the dosage form. The tensile strength measures the strength of the film as diametric tension or tearing force. Ongoing studies use this parameter to measure the mechanical strength of the films during formulation optimization. The sample under test is stretched until it tears and the stress needed represents the tensile strength [14]. It is calculated by dividing the force (N) at which the film breaks with the cross sectional area (m^2) of the film.

Several methods for measuring tensile strength of films have been investigated and reported in the literature. A TA.XT2 texture analyzer equipment equipped with a 5 kg load cell to determine the tensile strength of the prepared film was reported. Briefly, film strips were held between two clamps positioned at a distance of 3 cm. Then the strips were pulled by the top clamp at a rate of 2 mm/s and the force was measured when the films break [15,16].

In another method, Palem et al. used a microprocessor based advanced force gauze with a motorized test stand to assess the tensile strength of the buccal patches [17]. The strips from the patch were placed between two clamps to secure the patch. The lower clamp was held stationary and the strips were pulled apart by the upper clamp moving at a rate of 2 mm/s until the strip broke.

Tensile strength of buccal films was also determined by fixing the films between the stationary and movable plates of a tensiometer. The tensile strength of the film was determined by measuring the total weight loaded on the string to break the film [18].

The influence of plasticizer on the tensile strength of film was reported in several investigations. Hyppola et al. observed that the tensile strength of the films varies with the plasticizer, suggesting that the choice of the plasticizer is important to obtain the required tensile strength [19]. Reports also exist wherein the tensile strength of the film was inconsistent with increase in the concentration of mucoadhesive agents. The increase in carbopol content (30 to 50%) was found to decrease the tensile strength of buccal films prepared using sodium carboxymethyl cellulose, but resulted in softening of the film when the carbopol quantity was further raised (up to 70%) [15].

2.3. Young's modulus

Young's modulus or elastic modulus is the measure of stiffness of film. The methods used for the measurement of tensile strength could be utilized here as well. This measures resistance to deformation and can be observed by plotting the stress strain curve wherein the slope measures the modulus. The higher the slope, the greater is the tensile modulus. However, a gentle slope measures a low tensile modulus and case of deformation. Further if the modulus keeps on changing with stress, the initial slope gives the modulus, and is commonly observed in the case of plastic materials [20]. Moreover, films which are hard and brittle in general possess higher tensile strength and higher Young's modulus values.

2.4. Elongation at break and percent elongation

Elongation is a kind of deformation. It is a simple change in shape that anything undergoes when under stress, which can be measured using a texture analyzer. In other words, when a sample is put under tensile stress, the sample deforms, becomes longer or gets elongated [8]. A sample can be checked for either elastic elongation or ultimate elongation. Elastic elongation is important for all kinds of elastomers and is the percent elongation one can stretch a material without any deformation of the sample. Ultimate elongation measures the amount to which a material can be stretched before it breaks. When stress is applied to a sample piece, strain develops and the length of the sample increases with increase in the amount of stress applied. The point at which the sample piece breaks after a sufficient increase in length is referred as percent elongation break. Reports are available wherein the buccal films have showed percentage elongation up to 40% [21]. The percent elongation is generally calculated as: % Elongation = (Increase in length of film × 100 / Initial length of film).

It has been reported that the type and content of polymer, amount of plasticizer and drug have a profound effect on the percent elongation of the film [8]. For instance, sodium carboxymethyl cellulose films containing carbopol showed low elasticity while the hydroxypropyl