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Oral Films: A Look Back

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Oral films, a promising novel drug delivery system, are a strip of single or multilayered, mucoadhesive or non-mucoadhesive, thin polymeric films that are intended to deliver active therapeutic moieties either locally or systemically in oral cavity through sublingual, buccal, palatal, or gastrointestinal absorption [1-3]. In general, films are known by several names including but not limited to orodispersible films [4], orally disintegrating/dissolving films [5,6], rapid/fast/quick dissolving films [7-10], oral soluble films [11], oral thin films [12], strip films [1,13,14], quick disintegrating/dissolving films [8], buccal or buccal soluble film [15], mucoadhesive films [16], transmucosal films [17], sublingual films [18], etc. Strip films or thin films could be considered as a broad spectrum of classification or superset of films that might include all kinds of film applications for oral, topical/transdermal, vaginal, etc. Consequently, the focus of this topic, oral films, are generally strip or thin films intended for oral application, i.e., either oral cavity or gastrointestinal tract, and can generally be classified into oromucosal films and orodispersible films.

Oromucosal films are mucoadhesive in nature and are designed to adhere to sublingual, buccal, or palatal mucosa to deliver therapeutic moieties locally or systemically [19]. Oromucosal films could further be classified into buccal films, sublingual films, and palatal films according to their site of application and/or absorption. Oromucosal films that are aimed to deliver drugs systemically though sublingual, buccal, or palatal mucosa can be advantageous over orodispersible films due to their ability to bypass the first pass metabolism [2]. Orodispersible films are mostly non-mucoadhesive that disintegrate and/or dissolve immediately in oral cavity upon contact with saliva without involvement of water or chewing and deliver drugs locally or systemically through gastrointestinal absorption. Orodispersible films could further be subdivided into orally disintegrating films and orally dissolving films, based on their ability to disintegrate and dissolute in oral cavity, respectively.

In the film realm, there has been a lack of discriminatory line between orally disintegrating and dissolving films, and sometimes, if not often, the two terms are either misunderstood and/or misused. At this point in time, to understand them better, it would be beneficial to reiterate the fact that dissolution represents drug in solution (dissolved drug in saliva, *in vivo*) while disintegration represents breakage of film formulation (dispersion of film components in saliva). Both films, orally disintegrating films and orally dissolving films, should disintegrate or disperse in oral cavity to be claimed as orodispersible films. However, although it is an obligation for the orally disintegrating films to disintegrate in the oral cavity to facilitate fast dispersion in saliva for easy swallowing, dissolution of drug in oral cavity might not be crucial to achieve target therapeutic concentration for the films that are designed to be absorbed in gastrointestinal tract, as most of the dissolution and absorption of drugs would occur in gastrointestinal tract. Ironically, if the target site of action and/or absorption is oral cavity (mucosal, palatal, sublingual, buccal), then dissolution in oral cavity becomes an essential component and the formulation must be an orally dissolving film.

Furthermore, the solubility of the drug could play a vital role in determination of disintegration vs. dissolution of films in oral cavity. Dissolution of aqueous soluble drugs that belongs to BCS Class I/III in mouth or oral cavity could occur simultaneously with disintegration of films despite they were designed to be absorbed in gastrointestinal tract. This is because of the intrinsic dissolution of drug itself in water (saliva) rather than the impact of formulation component. On contrary, dissolution of poorly aqueous soluble drugs in oral cavity that belongs to BCS Class II/IV could be difficult given their poor solubility and intrinsic dissolution rate, and limited amount of saliva in the oral cavity. The films containing these poorly water soluble drugs are in general orally disintegrating films, whose target site of dissolution and absorption is gastrointestinal tract. Consequently, orodispersible films could either be orally disintegrating or dissolving films depending on the intended site of action and/or absorption. Whatever the intention, when the film is termed as orally dissolving, it should deliver the drug in solution form upon introduction into oral cavity.

Until recently, it was the consent of film formulators that oral films could only be used for delivery of water soluble drugs given their size and thickness. Fascinatingly, recent works have demonstrated the possibility of incorporating poorly water soluble drugs (BCS Class II/IV) into films with faster dissolution [10,13,20,21]. On one hand, although incorporation of poorly water soluble drugs into films seems promising, the dissolution of the poorly water soluble drug particles in *in vivo*, especially in oral cavity, is a matter of concern if the target site of action and/or absorption is oral cavity. On the other hand, as mentioned earlier, dissolution of poorly water soluble drugs in oral cavity might not be crucial for films if the target site of dissolution and absorption is gastrointestinal tract. Hence, the issue of dissolution of poorly water soluble drugs in oral cavity is out of concern, and in fact, these recent findings open a whole new venue of opportunities. In general, like any other drug delivery systems, the rate and extent of dissolution and target site of absorption for oral films could be tailored by its components.

The components of film formulation could include, but not limited to, the polymers that form the film matrix, plasticizers that improve the mechanical properties of the film, viscosity enhancers that improve the viscosity of the film precursor solution/suspension, disintegrants that improve the disintegration of the film, stabilizers or surfactants that improve the wetting and/or drug particle suspension, other additives such as sweetening agents, saliva stimulating agents, coloring agents, etc. [1-3,19]. Among these, polymers and plasticizers are the major constituent of film formulation and selection of which is very

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critical given its significant effect on film performance in terms of disintegration and dissolution, and mechanical properties in terms of tensile strength (hardness) and Young's modulus (brittleness). Among various techniques and technologies available for film manufacturing, solvent casting and hot melt extrusion have been widely used [1,22]. Recently, new techniques such as semisolid casting, solid dispersion extrusion, rolling, etc. are also being considered for film preparation [22]. Aqueous slurry casting, another variation of film casting technique, has been gaining attention recently due to the possibility of film manufacturing without the use of expensive and harmful solvents [10,20]. In addition to these, new innovative techniques like printing and spraying deserve to be noted [23,24]. The manufactured oral films could be characterized for various properties like, organoleptic characteristics: appearance, size, shape, color, transparency, taste, odor, pores, tackiness, etc.; mechanical properties: tensile strength, Young's modulus, elongation at break (percentage elongation), tear resistance, folding endurance, swelling property, etc.; performance attributes: assay, content uniformity, impurities, disintegration, dissolution, residual water and/or solvent content, microbial content, etc. [1-3,22].

Among the above mentioned characterizations, the organoleptic characteristics are mainly focused on the patient acceptability. So, as long as the shape, size, color, and taste, etc. are acceptable to patients, this would not pose any threat in regards to film integrity or performance. The mechanical properties of oral films must be maintained at appropriate level for easy manufacturability as well as for proper handling and transportation during process and by patients. Although the appropriate value of mechanical properties varies from one film to another due to the variation in composition, drug load, and dosage form design, Preis et al., reported that the mechanical strength of orodispersible film can be best characterized by achieving puncture strength of at least 0.08 N/mm^2 and elongation at break of around 1.03-6.54%, based on investigation on various commercial products [25]. According to the literatures, the measurement of disintegration of oral films have been investigated widely in three different methods, (1) Standard USP disintegration tester apparatus with or without modification [26], (2) Petri dish method without various types/volumes of medium (measures time taken for the film to dissolve when placed on top of a small volume of medium) [5], (3) Slide frame method (measures time for a single drop of water, deposited on a film held securely in the horizontal direction, to disintegrate/dissolve and make a hole) [27]. Unfortunately, all of the above-mentioned methods face challenges mainly with the end-point determination of the disintegration process, leading to inconsistencies in disintegration time. Likewise, although USP apparatus I (Basket), II (Paddle) and IV (Flow-Through Cell) are available to investigate the dissolution of oral films, there is no clear understanding or guidance on dissolution method of choice, with possibility of mimicking or simulating the oral cavity with little saliva (water or bio-relevant media) and presence of mechanical stress of tongue and palate on films upon introduction. Furthermore, the presence of saliva stimulating agents in oral films might cause additional concerns as the saliva secretion could vary between people depending upon age, disease condition, and/or type/amount of medications taken. Above all, since the oral films could be incorporated with micro-/nano-particles of poorly water soluble drugs, it is a reasonable expectation that the dissolution method to have higher discriminative power to test the particle size as well as formulation effects. Recently, one of the studies demonstrated the superior discriminatory power of the USP IV and suggested that it could be employed as a testing device in the development of strip-films containing drug nanoparticles [28]. The film formulators would agree that the USP prescribed disintegration or dissolution test for solid dosage formulations like tablets and capsules cannot be directly applied to oral films due to the variations in dosage form and challenges associated with end-point determination. Therefore, this is the high time that necessitates a well-suited discriminative disintegration and dissolution test method for oral films.

In general, oral films have myriad of advantages over the conventional formulations in terms of performance characteristics such as availability of larger surface area for faster wetting, disintegration, and dissolution; clinical advantages such as dosing accuracy and flexibility; pediatric and geriatric patient-friendly characteristics such as ease of administration without the necessity of water, chewing, and swallowing, and ease of portability and handling; manufacturability factors such as robustness with process handling, and possibility of powderless aqueous-based solventless film manufacturing with enhanced continuous processability [2,3]. While the oral films hail the above-mentioned accolades, the major limitations associated with them are difficulty in incorporating poorly water soluble drugs, relatively smaller drug load given its smaller size and thickness, and sensitivity to humidity and temperature necessitating exclusive packaging [2,3]. Optimistically, recent studies have been addressing various limitations of oral films such as possibility of incorporation of poorly water soluble films into oral films by various particle engineering techniques [10,13,20,21].

Given its potential benefits oral films could soon be an alternative to the currently available formulations. Furthermore, oral films could be a life-saver for numerous patent expiring drugs, as approval of oral film application will garner three-year market exclusivity period given its novelty and type of application [new dosage form, 505 b(2)]. It is not too far that all the limitations associated with oral films were addressed effectively by the film formulators, and eventually, the oral film platform technology will be "delivery system of choice" for the all, especially to the pediatric and geriatric patient population. Most of all, incessant introduction of innovative films into market by pharma companies itself vouch for their acceptance by pharmaceutical industry, healthcare professionals, and of course, by patients.

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