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Teaser The technological and biopharmaceutical improvements of orodispersible dosage forms are reviewed in the light of regulatory requirements.

Orodispersible dosage forms: biopharmaceutical improvements and regulatory requirements

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Orodispersible dosage forms have a growing presence in the pharmaceutical market because their administration can improve the bioavailability of some drugs and their prescription can ameliorate patient adherence and/or compliance. Here, we review the main features of orodispersible tablets, including oral lyophilisates, and orodispersible films along with their main production technologies. We summarize the bioavailability data and critically discussed their potential to improve patient adherence and/or compliance. We revisit this information in light of both the European Union (EU) and US regulatory frameworks, focusing on the differences in the definitions of such dosage forms and the requirements for marketing authorization.

Introduction

Different dosage forms have been proposed to maximize the therapeutic potential of the active pharmaceutical ingredient (API) and facilitate its access to patients. Liquids (i.e., syrups, suspensions, and solutions) can be easily swallowed and, in most of the cases, guarantee the largest bioavailability, although the dose accuracy is limited by the use of spoons or syringes to measure the volume to be administered. Thus, to overcome this limitation, single-dose sachets (i.e., a unit dose packaging), containing a defined dose as powder, granules, or effervescent tablets dissolving and/or dispersing in water, have been introduced. However, the market is currently dominated by tablets and capsules. Indeed, both dosage forms allow the delivery of an accurate dose of the API and are capable of being economically mass produced. Nevertheless, the administration of tablets or capsules is often associated with swallowing problems or fear of chocking and, thus, there is a growing number of situations in which these products are not patient acceptable. Indeed, it is estimated that 20% of the population have psychological or physiological impairments that prevent them from swallowing tablets or capsules. This is particularly relevant for children, older patients, and patients with dysphagia [1]. Other groups that might experience problems using conventional oral dosage forms include patients with a mental illness, and those who are nauseous or uncooperative, as well as patients with reduced liquid-intake plans and travelers

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who might not have access to water [2]. To solve this issue and guarantee the benefits related to solid-dosage forms, orodispersible-dosage forms (ODx) are gaining increasing interest.

An ODx is defined as a dosage form intended to be placed in the mouth, where they rapidly liberate the loaded API to produce a fine suspension or solution of it in the saliva. Thus, ODx improve patient compliance because they are easily swallowed without drinking or chewing, and assure accurate dosing compared with liquid-dosage forms. In addition to improving patient compliance and/or adherence, ODx can modify the pharmacokinetic parameters of the API according to its physicochemical features. For example, the extent of absorption of selegiline is significantly increased [2], while the bioavailability of piroxicam remains unaffected after administration using an ODx or an immediate-release tablet [3].

Nevertheless, there is little published on the use of ODx, despite the increasing applications for marketing authorization for such products. Here, we briefly describe the main features of orodispersible tablets (ODTs), including oral lyophilisates, and orodispersible films (ODFs) as well as their main production methods. We summarize the published bioavailability data and their potential to improve patient adherence and/or compliance, in light of EU and US regulatory frameworks.

The design of orodispersible dosage forms

The development of an ODx requires specialized production methods and/or particular excipients, which are intellectually protected and/or require specialist knowledge. Two main ODx currently available on the market are ODTs and ODFs. Acceptance of either form by a patient is related mainly to their taste. Present approaches to masking taste in ODx technologies include sweeteners and flavorings, microencapsulation, or complexation [4]. Moreover, the balance between disintegration time and mechanical hardness of the ODx is intricate and affected both by process and formulation variables. Thus, the packaging design is usually optimized to protect the final dosage form from environmental moisture and/or mechanical stresses.

Orodispersible tablets

ODTs are similar in appearance to conventional tablets; the rapid penetration of water through capillary action into the porous framework leads to their disintegration in the 30 s–3 min range [5,6]. The main production strategies include lyophilization, molding, or direct compression using specific excipients.

Freeze-drying is a key process in the production of ODT. Solvent sublimation from a frozen solution or suspension of an API with matrix-forming excipients generally results in a porous and lightweight product, which dissolves instantly to release the API when placed in the mouth. In terms of poorly water-soluble APIs, freeze-drying can also help achieve a final product with the desired physical or chemical characteristics by reduction of crystal size or conversion from the crystalline to the amorphous form [7]. Moreover, because low-operation temperatures minimize API thermal degradation, this technology was recently proposed for use in the development of ODT-containing vaccines [8]. For example, Zydis® tablets are produced by freeze-drying after dispersing and/or dissolving the API in a water-soluble material directly in the blister [2]. Typical matrix-forming excipients include gelatin, dextran, or alginates. Mannitol is often used to increase the fluffy volume of the lyophilisate and glycine is used to prevent shrinking during freeze-drying. The ideal drug candidates have low water solubility, with fine particles (<50 μm) and good aqueous stability in the suspension. For water-soluble APIs, the maximum drug loading is approximately 60 mg [1].

Compression and heat molding are the main approaches to preparing ODTs using a molding technique. The former involves moistening of the powder blend with a hydroalcoholic solvent, followed by compression into mould plates to form a wetted mass, which is then air-dried. During the heat molding process, a molten mass containing a dispersed and/or dissolved drug is directly poured onto blister packaging. Then, the dispersion is solidified at room temperature.

In both cases, molded tablets have a highly porous structure, which increases the disintegration and dissolution rates. However, the addition of binders is often required to provide sufficient mechanical resistance and prevent the tablets from breaking. The dissolution and/or dispersion time of the API depends on its physical state in the matrix. By contrast, the API can also dissolve partially or totally in the molten carrier, forming either a solid solution or a suspension in the matrix, respectively [9].

Compression is a straightforward method of producing ODTs with good mechanical strength. However, the relatively low porosity of a tablet matrix can reduce water penetration, prolonging the disintegration time. The formulation methodologies to produce mechanically acceptable ODTs include the use of excipients that can induce fast disintegration (e.g., effervescent agents or superdisintegrants [10]) or sublimation agents (e.g., menthol, camphor, thymol, and ammonium bicarbonate [11]) or melting binders (i.e., binders that melt at body temperature [12]). Among the market-available products, Durasolv® and Orasolv® technologies are based on direct compression with or without effervescence excipients, which make possible a dose ranging from 0.125 mg to 500 mg and 1 mg to 750 mg, respectively.

Crystalline transition methods involving low compression forces to ensure high tablet porosity followed by postmanufacture treatment (i.e., heat or humidity) were also proposed to produce hard tablets without compromising disintegration time [13,14]. However, variations in the solid state of the drug limit the application of these approaches [12].

Particle engineering by means of blending [15], co-grinding [16], and freeze-drying [7] allows the design of new multifunctional excipients with improved mechanical or disintegration properties without developing a new chemical entity. As an example, the granulation of a low compressibility saccharide, such as mannitol, which provides fast disintegration, with a high compressibility saccharide, such as maltose, produces strong compacts with high tensile strength and fast disintegration time [15]. When freeze-dried amorphous sucrose mixed with mannitol was compressed at low compression strength, crystallization of the amorphous sucrose in the tablet occurred, increasing the tablet tensile strength without altering the original tablet porosity [13]. Moreover, spray drying is considered a valuable tool for the development of tablets containing multifunctional excipients with improved flowability and porosity [12]. Similarly, freeze-drying produces hybrid excipients with high porosity and specific surface area [7].

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