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Infarma CIÊNCIAS FARMACÊUTICAS

Revisão

The popularization of orodispersible tablets in the pharmaceutical market

A popularização dos comprimidos orodispersíveis no mercado farmacêutico

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ABSTRACT

Orodispersible tablets are getting popular due to its easy administration which leads to a higher therapeutic adherence. This study aimed to evaluate the state of the art of these drug products based on the scientific literature. Also, orodispersible tablets available in the US, Europe and Brazil markets based on information extracted from the health agencies were analyzed. Those tablets are designed to be placed on the tongue and instantly disintegrated by the fast capitation of the saliva without the additional intake of water. The orodispersible technology enables oral administration of tablets to patients with dysphagia, especially children, and elderlies. Moreover, orodispersible make possible rapid drug intervention and mouth absorption. The drug is partially absorbed in the oral cavity, pharynx, and esophagus without first pass effect, increasing drug bioavailability and reaching faster therapeutic effect. This is a low-cost technology that fits in a conventional solid production area and adds value to the product without requiring high investment. A market analysis showed there is a predominance of antihistamine drugs or medicines for mental disorders using orodispersible matrices. However, the orodispersible technology shows great versatility and potential application to other pharmacological groups. It is expected that in coming years a massive commercial insertion of this tablet technology occurs. In this scenery, it is indispensable that health professionals are prepared with updated technical information for the use of this therapeutic resource safely and efficiently.

Keywords: orodispersible tablets; oral absorption; dysphagia; therapeutic adherence

RESUMO

Os comprimidos orodispersíveis têm ganhado popularidade por serem de fácil administração e levarem a uma maior adesão terapêutica. Esse estudo teve como objetivo avaliar o estado da arte desses medicamentos com base na literatura científica. Adicionalmente, foram levantados os comprimidos orodispersíveis disponíveis nos mercados dos EUA, Europa e Brasil com base em informações extraídas das agências sanitárias dessas regiões. Esses comprimidos são concebidos para serem colocados na boca e instantaneamente desintegrados pela captação da saliva, sem a necessidade de água. A tecnologia orodispersível viabiliza a administração oral de comprimidos em usuários com disfagia. Adicionalmente, esses medicamentos possibilitam uma rápida intervenção medicamentosa e absorção bucal, fazendo com que uma fração do fármaco seja absorvido na cavidade oral, faringe e esôfago sem sofrer efeito de primeira passagem, incrementando sua biodispobibilidade e permitindo alcançar um efeito terapêutico mais rápido. O barateamento dessa tecnologia, que se adapta a áreas de produção de sólidos convencionais, agrega valor ao medicamento sem demandar alto investimento.

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Um levantamento dos orodispersíveis existentes no mercado atualmente mostra que há um predomínio de medicamentos para transtornos mentais e de anti-histamínicos, contudo, a tecnologia orodispersível revela versatilidade e grande potencial de aplicação para inúmeros grupos farmacológicos. Espera-se que nos próximos anos haja um aumento da inserção desse tipo de comprimido, principalmente em mercados com menor penetração desses medicamentos atualmente como o Brasil, sendo imprescindível que os profissionais de saúde estejam munidos com informações técnicas atualizadas para a utilização desse recurso terapêutico de forma segura e eficiente.

Palavras-chave comprimidos orodispersíveis; absorção oral; disfagia; adesão terapêutica.

INTRODUCTION

The pharmaceutical industry invests billions of dollars in the development of new medicines. It is one of the industrial fields that most invest in innovation. Worldwide, the total spend on research and development by pharmaceutical and biotechnology companies in 2015 were 141 billion dollars. Among the 50 companies that invest in research and development in the fiscal year of 2014/2015 were 16 pharmaceutical companies (1) . The consequence of this hard investment is the high number of patents and different drug delivery devices developed, which includes nanostructured systems and even smart delivery matrices (2).

Although the high potential of those technologies just a small amount reaches the market. The registration of new drug products has been declining a lot in the last decade. The reasons for that are complex and involve the high development cost, besides the hardship production in a large amount, and the regulatory barriers for registration of this new technologies (3).

In this context, from medicine industrialization in the XX century until nowadays, solid oral dosage dominate the pharmaceutical market (4). The adaptation to an industrial production, the low cost, and the patient's acceptance are some of the advantages that make tablets the most commercialized on a global scale (5). From that, it is coherent infer that the introduction of new technologies related to this dosage form have high possibility of commercial success. In the last years, a new technology entered the market of tablets without flaunt; however, with perspectives of leveraging the market, the orodispersible tablets.

Orodispersible tablets, also called tablets of instant dissolution, are non-coated tablets elaborated to disintegrate fast when put over the tongue as the Figure 1 shows (6,7). The benefits of this technology include the easy administration, after all it does not need to be chewed and does not need liquids to be swallowed (8). The goal of this review is to draw a panorama of the orodispersible pharmaceutical market nowadays addressing pharmacological, pharmacotechnical and functional aspects of this new kind of drug product.

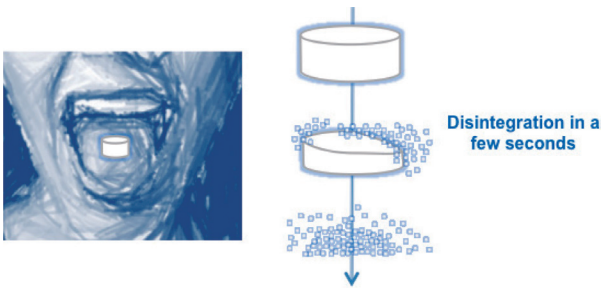

Figure 1. Diagram showing the administration of orodispersible tablets and the simulation of their rapid disintegration in the oral cavity.

METHOD

A search was made in scientific articles about the state of the art of orodispersible drug products in the *Scifinder Scholar* database (https://scifinder.cas.org) using the keywords *orodispersible tablet, orally disintegrating tablet, mouth dissolving tablet, fast dissolution tablet and fast disintegrating tablet*.

In addition, a survey of the commercial orodispersible tablets available in the United States, European Union, and Brazil were performed based on the search of the records from the health agencies of each region. Specifically, the databases from Food and Drug Administration – FDA/ United States (https://www.fda.gov); European Medicines Agency - EMEA/ European Union (http://www.ema.europa.eu/); and National Agency of Health Surveillance – ANVISA/Brazil (http://portal.anvisa.gov.br/) were consulted. Moreover, the health agency of the United Kingdom (https://www.gov.uk/) besides the website of big pharmacy companies from the North America (https://www.drugs.com) were also verified.

RESULTS AND DISCUSSION

Benefits of the orodispersible technology. The use of orodispersible tablets improves the treatment by the readiness administration. This kind of tablets dispenses the use of water being designed to disintegrate instantly in the mouth by simple contact with saliva. This convenience leads to a higher treatment adherence and to better clinical results (8–12). The value of this technic includes convenient administration in every day situations in which it is difficult to get water, for example when the patient is traveling or when he is in a work that can not be interrupt. Moreover, it might be decisive when the administration of the drug is urgent (13,14).

Patients with dysphagia, can be hugely benefited by the use of orodispersible tablets, between those are children, elderliers, (8,15), people who have mental disorders as Alzheimer (16,17) or Parkinson's disease, besides non cooperative patients as the ones that are bedridden, traumatized, nauseated or with any other disease or circumstance that difficult or prevent their ability to swallow tablets (18,19). In these cases, orodispersible eliminate the risk of suffocation for obstruction that might be caused by the use of conventional tablets (13,20–22).

Another important aspect in the technology of orodispersible involves the anticipation of pharmacological action of the drug. The prompt disintegration at the mouth possibilities a partial or total solubilization of the drug leading to a pre-gastric absorption. In this way, the drug starts to be absorbed at the oral cavity, pharynx and esophagus generating a fast therapeutic effect without liver metabolism, increasing the bioavailability of the medicine (23). In addition, it prevents the drug to be degraded by the acid pH of the stomach or for the pancreatic enzymes. This might lower the dose of the drug needed to a get the therapeutic effect and consequently reduces the adverse effects (9,24). It stands out that the fast pharmacologic effect propitiated by this technology might be decisive for the therapeutic purpose, as in an allergic process in which the patient needs an antihistamine as soon as possible.

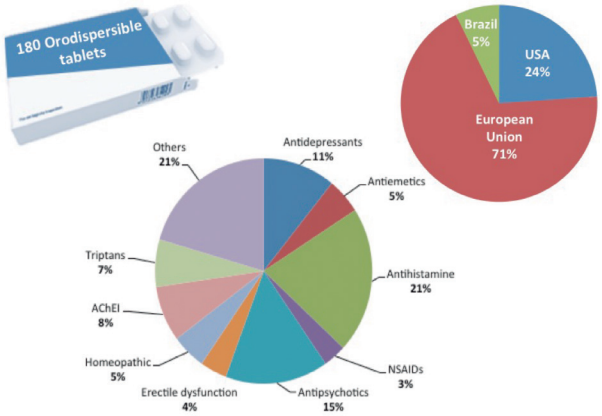

Figure 2. Total drug products commercialized as orodispersible tablets in the Brazilian, European, and North American market and their percentage distribution by geographic region and by pharmacological class.

Orodispersible tablets market. Some of the published market surveys show that the orodispersible tablets market is in a high expansion. It is estimated that this segment is growing almost 20% per year (4). This paper explored the orodispersible tablets available in the United States, European Union, and Brazil.

It was found 180 orodispersible drugs commercialized in these markets above mentioned. The European market has the highest number of drugs using this technology, 124. In the United States it is possible to find 43 orodispersible medicines, while Brazil has just 13.

The distribution of medicines using this technology divided by pharmacological class is showed in the Figure 2. It is observed that the orodispersible technology has quite diverse pharmacological applications. The pharmacological groups that have more medicines using the orodispersible technology are the antihistamine (21%); medicines for mental disorders as antipsychotics (15%), antidepressants (11%), acetyl cholinesterase inhibitor (AChEI) (8%); and drugs used to treat migraines such as triptans (7%).

Groups that have conclusive therapeutic benefits with orodispersible technology were more found in the survey. This is the case of antihistamines such as desloratadine and ebastine. These drugs are usually given to control allergic attacks, so anticipating the onset of the drug's effect may be critical for containing

the progression of the allergic process, avoiding further complications (4,21).

Medicines for mental disorders as olanzapine and risperidone, which are a third part of the orodispersible available in the market, have as target patients who have trouble swallowing tablets and do not usually co-operate with the administration. Acetyl cholinesterase inhibitors, as donepezil, are used to Alzheimer's treatment in elderlies that found complicated to swallow tablets, especially those who are in advanced stages of the disease. In such cases, the facilitated administration of orodispersible may be determinant for therapeutic compliance.

Medications used for pain, such as triptans, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) add up 13% to the total of orodispersible drugs in commerce. In these cases, the onset of the faster effect will allow pain relief in a shorter time compared to conventional tablets. This class of drug has a wide spectrum of users and the therapeutic advantage of having a faster effect might be decisive to the patient's choice of tablets containing orodispersible technology (4,9). The administration of antiemetic in the form of orodispersible tablets also seems to assign clear advantages to nauseated patients in which the ingestion of liquid could induce vomiting before the drug effect.

Moreover, the use of orodispersible tablets in the homeopathic market shows 9 industrial presentations, besides the use of this technology for the treatment of erectile dysfunction as in orodispersible tablets having sildenafil. In these case, the advantages of easy administration and fast effect are important to the user who wants to maintain the reticence regarding its use and also need its effect just after administration (13).

Production technology. The first patents involving pharmaceutical forms of orodispersible were registered in the ninety-decade of the last century, however this technology showed a higher development in the last ten years, with dozens of scientific works published in this period and many products placed in the market (4,25). Besides the therapeutic benefits of orodispersible tablets, they are easily adapted to industrial scale and have low cost of fabrication (24,26). There are unnumbered methodological variations and possibilities of materials to the production of these tablets. The majority fabrication process demands the existing machinery and industrial area in a common solids manufacturing plant

In general, regardless of the technology employed, what is intended is to produce a highly porous solid matrix. The Figure 3 shows in detail the pores found in the matrix of these tablets. This feature allows a rapid uptake of saliva into the tablet to disintegrate it (13).

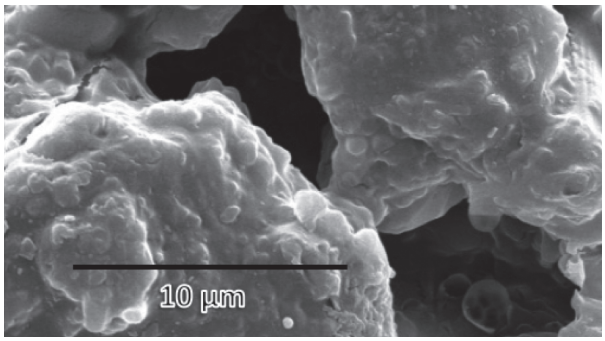

Figure 3. Photomicrograph obtained by scanning electron microscope of the cross-section of an orodispersible tablet produced by lyophilization.

The most commonly cited production processes for the production of orodispersible tablets are:

Lyophilization: In this process, which is one of the most used, the formulation is in a form of aqueous dispersion that is frozen, and after that the solvent is removed through sublimation. The drug might become amorphous in this process, which contributes to its rapid dissolution (22). The freezing of the formulation and its sublimation can be done directly in the primary container. The tablet obtained does not go through a traditional compression process, and it is compressed by a process called pseudo-compression. This technique presents intermediate complexity and produces a matrix of high porosity and very low mechanical resistance (25).

Sublimation: This technic is based on the use of inert volatile substances, as urea, camphor, and ammonium bicarbonate for the composition of the tablet. After the compression process, the tablets are heated so the volatile substances are removed by sublimation, and it leaves pores in the tablet matrix (24,27,28).

Extrusion: the formulation goes through a mechanical process and simultaneous heating being extruded through a die. The extruded is cut or pulverized and subsequently compressed. This technology produces tablets of high aqueous solubility and good mechanical resistance (29,30).

Molding: The components of the formulation, in general water-soluble sugars, are moistened with a hydro-alcoholic mixture and subjected to a low pressure (molding) compression process. The tablets are then exposed under vacuum to remove the solvent. This process originates porous matrices of low physical resistance (13).

Without Water Tablet Method (Wowtab®): This is the classic technic of orodispersible obtainment being one of the first to be patented. It consists in the obtainment of tablets through wet granulation with high percentage of sugars as mannitol, sorbitol, lactose and sucrose. These tablets are exposed to a high relative humidity (85%), so the hygroscopic matrix starts to uptake a high amount of water. This step is followed by the exposure of these humid tablets to a heat of 40°C and low relative humidity (30%). The result of this process is the removal of the previously collected water and the attainment of a highly porous matrix with intermediate mechanical resistance (9,24,31).

Conventional compression: This technic is based on the direct compression of the formulation or on the compression of wet or dry granules (32). These orodispersibles disintegrate due to the presence of superdisintegrator, such as croscarmellose, crospovidone, sodium starch glycolate and calcium silicate (33), or due to the effect of effervescent components (34), added to the preparation in high concentration. Moreover, there is an addition of sugars of high aqueous solubility, such as mannitol, dextrose, fructose and lactyl that promote disintegration as well. The tablets obtained in that process have characteristics very similar to a conventional tablet, including high mechanical strength. They are produced in conventional compressors and can be packaged in standard blisters.

Problems with orodispersible technology. There are some inconvenient that might be more or less accentuated depending on the technology of production or the formulation of orodispersible tablets (13). Some components in orodispersible tablets, as sugars, are highly hygroscopic which might lead to stability problems due to water capitation, especially after withdrawal of the pill from its primary packaging. An airtight container is a sine qua non condition to maintain the stability of these tablets.

Some preparations contain poorly water-soluble diluents, such as microcrystalline cellulose and dicalcium phosphate, which leave solid waste in the mouth, leading to an unpleasant sensation in the users. This problem can be solved by replacing these components for soluble diluents, such as mannitol (35).

The unpleasant drug flavor is also a problem, and it is tough to be bypassed since this medicine is thought to disintegrate in the mouth, which invariably, promotes contact of the drug with the taste buds. Polymeric coats, drug micronization, or complexation with cyclodextrins are some of the alternatives that might completely solve this drawback (13,16,36).

Another problem is that some of the production process form low mechanical resistance pills, as the ones produced through lyophilization. Moreover, there is an aggravating factor, the low mechanical resistance makes those tablets inadequate to subdivision for dose adjustment, as it is done in conventional tablets (5). In such cases, the primary packaging should be adapted to avoid matrix breaking during transport and handling (8). For avoiding this problem it is possible to obtain more resistant matrices with the use of disintegrating and diluents agents coprocessed or with the optimization of the compression conditions (35,37).

Innovations in the orodispersible technology. Orodispersible technology have been designed to proportionate the immediate liberation of drugs, however recent studies show the possibility of applying this technology to produce retarded or sustained release of drugs using in orodispersible matrices. The purpose is reducing the number of daily doses of medicines maintaining the plasmatic levels of drugs without high fluctuation. The use of functional polymeric nano and microparticules and ion exchange resins are among the technological strategies exploited for this purpose (38,39).

Orodispersible tapes appear as one of the latest innovations on this field. They ally advantages of orodispersible tablets as the easy administration and fast action with the possibility of dose adjustment. Orodispersible tapes are polymeric films for oral administration that have one or more layers. The dose might be adjusted through the size of the tape (Figure 4). One of the first medical devices using this technology was launched in the United States market in 2003 - Chloraseptic relief strips®, which is a fast-dissolving tape containing local anesthetics for throat inflammation. The industrial production of these devices might use the assembly lines of transdermal patches (38,40–42).

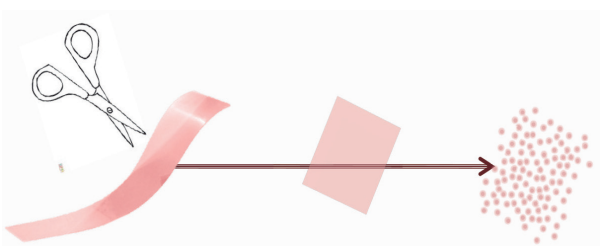

Figure 4. Scheme of an orodispersible tapes which can have its dose adjusted through the size of the tape and its mouth disintegration.

Another new approach in the orodispersible technology is the production of orodispersible mini tablets (tablets with a diameter of 3 mm or less). They are produced in a conventional solid manufacture just with simple tool adjustment. Besides its possibility of dose adjustment, orodispersible mini tablets are more convenient than conventional tablets especially for children and showed to be more accepted than syrups by children of the age of six months to five years (43). Moreover, they have the advantages of using a solid formulation, as the good stability and low cost of transportation and storage (44).

In addition, innovation in the orodispersible technology might be found in its production. In 2015, US Food and Drug Administration (FDA) approved an orodispersible drug called Spritam® a new presentation of levetiracetam from Aprecia Pharmaceuticals that is produced using powder-liquid three-dimensional printing. The technique patented as ZipDose by Aprecia consists in a multi layer tablet made using powdered formulation with liquid bonding followed by another layers of powdered formulation in order to create a highly disintegratable tablet. This technology allows the production of tablets with high doses of drug - up to 1000 mg (45).

CONCLUSION

Orodispersible tablets got the pharmaceutical market in the last decade with the promise of improving bioavailability of drugs and increase therapeutic compliance. This technology was used mostly for drugs to treat mental disorders, antiallergic and analgesics reaching high popularity in the American and European market mostly with patients with dysphagia besides children and elderlies. Nowadays, the abridgment of the production process of this technology and the patent drop of several drug product produced through this technology makes the scenario very prone to the massive use of orodispersible tablets in the global pharmaceutical market.

Considering the benefits showed it is not overweening to say that the orodispersible technology might be the difference between an effective treatment and a therapeutic failure for some patients. In this way, it is important that health professionals as pharmacists, physicians and nurses, as well as caregivers know details of orodispersible drug products, so they can explore its potential in benefiting patient's health.

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