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Review paper

Production technologies and formulation strategies in development of orodispersible tablets (ODTs)

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Abstract

One of the new ways of drug delivery that is being developed more and more often recently is orodispersible tablets (ODTs), also known as orally disintegrating tablets, rapidly dissolving tablets and fast-dissolving tablets. The European Pharmacopoeia (Ph. Eur.) defines ODTs as uncoated tablets intended to be placed in the mouth where they disperse rapidly before swallowing, disintegrating within 3 minutes. ODTs come with many advantages such as: easy swallowability especially for paediatric, geriatric and bedridden patients, as well as for people with lack of access to water; fast release of API and fast onset of action; and enhanced bioavailability. Many of the novel drug delivery systems are difficult to scale-up and adapt to industrial production, and one of the many benefits of ODTs is that there are ways to manufacture them with conventional technology, which makes them cost-effective. All of these advantages lead to improved patient compliance. This review discusses the advantages and disadvantages of ODTs, the available production technologies including patented technologies, the main challenges in formulation of ODTs and different approaches for solving them, and where the research into ODTs as a novel drug delivery system is headed.

Key words: orodispersible tablets, advantages/disadvantages of ODTs, production technologies, patented technologies

Introduction

The route of drug application is the way through which the dosage forms are administered into the human body. Various routes have significant role in drug bioavailability and the selection of the administration route depend on the drug physicochemical properties and its pharmacokinetic and pharmacodynamic profile (Kim and De Jesus, 2023). Oral administration is the most common and preferable route for drug administration, by the patients and by the physicians. It provides easy application, safety, comfort, good patients compliance and adherence to the therapy. In order to address to patients' needs for compliance, comfort and easy to use characteristics, different oral dosage forms are formulated and produced. Types of oral dosage forms according to European Pharmacopoeia (Ph. Eur. 11.5) are presented in the Table 1.

The Ph. Eur. 11.5 defines different oral dosage forms, among which tablets are the most prevalent form of solid dosage products. Their diverse range includes conventional (fast-release), as well as modified-release tablet with extended or delayed drug release.

Orodispersible tablets (ODTs)

According to Ph. Eur. 11.5, orodispersible tablets (ODTs) are defined as uncoated tablets intended to be placed in the mouth where they disperse rapidly before swallowing, disintegrating within 3 minutes. Due to the rapid disintegration, they provide fast release of the active

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pharmaceutical ingredient (API) and are preferable forms especially in paediatric, geriatric, paralysed, psychiatric and bedridden patients. In general, patients' acceptance of the treatment and compliance to the treatment could be improved by using ODTs mainly due to the pre-gastric absorption of the API, thus enhancing oral bioavailability and reducing dose frequency (Parkash et al., 2011). ODTs are limited to low dose API (generally less than 50 mg), but in recent years a lot of research is done to improve drug loading capacity, taste and stability in various packaging conditions.

In the oral cavity there is a large mucosal membrane region that offers an attractive route for administration of the API with desired systemic effect. The mucosa in the mouth is rich with blood vessels, has a relatively permeable membrane, and provides routes for absorption that overcome hepatic first-pass elimination. Also, the process of metabolism in gastrointestinal tract (GIT) is avoided, thus the absorption variables of the GIT mucosa could be overcome. By balancing the right dose of API, as well as design and components in the formulation, ODTs with differing characteristics could be prepared.

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Advantages of ODTs

As other oral solid and/or liquid dosages forms, ODTs provide all advantages that these forms have, along with some additional advantages like:

1. ODTs have good stability, provide accurate dosing, easy manufacturing, small size packaging, and easy handling by the patients. The manufacturing process is as similar as other solid forms and the packaging is practical and easy to manage.
2. Disintegration of the ODTs requires low amount of saliva, with no additional water. So, there is no risk of low adherence to the treatment dependable of access to water.
3. Easy to use administration provides comfort in use in paediatric, geriatric, hospitalized and institutionalized patients.
4. Fast disintegration and fast absorption will provide rapid onset of action, especially desired in patients that require therapy for neurological diseases.
5. Variety of clinical studies showed increased bioavailability of drugs absorbed by the pre-gastric mucosa (oral cavity, pharynx or oesophagus).
6. Due to the pre-gastric absorption, decreased first pass metabolism could be achieved, as well as avoidance of metabolism in GIT, and dependable absorption in small intestines (Suresh et al., 2008).

Disadvantages of ODTs

1. ODTs are hygroscopic in nature so they must be kept at controlled temperature and humidity. Almost all of them are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which implies for specialized product packaging. In production planning process, development of ODTs should take into consideration packaging design in the initial stages of development.
2. ODTs are designed for fast disintegration, usually less than a minute, so the designed tablets are with insufficient mechanical strength. ODTs are fragile, so external packaging must provide support for stability during transport and handling by the patients. Increasing mechanical strength can increase disintegration time, so a balance between those parameters must be obtained.
3. Taste and after taste in mouth are crucial factors for the good formulation of ODTs. Novel flavours and additives should provide an acceptable taste for the ODTs and lower "bitter taste" image. Addition of menthol and child friendly flavours can provide better compliance for the patients.
4. ODTs should disintegrate proportionally, without leftover residue in the mouth after the disintegration.

API formulated as ODTs

Representatives from almost all categories of API could be used in formulation of ODTs as dosage forms (Table 2.). Even vaccines and vitamins have been formulated as ODTs, in order to provide a more convenient and cost-effective delivery system for oral delivery by helping the distribution and access to patients (Tian Y et al., 2020, Wilkhu et al., 2017).

Table 1. Types of oral dosage forms according to Ph. Eur. 11.5

DOSAGE FORMS	
Capsules (Capsulae)	Hard capsules Soft capsules Gastro resistant capsules Modified – released capsules Cachets
Chewing gums, medicated (Masticabilia gummis medicate)	
Granules (Granulata)	Effervescent granules Coated granules Modified release granules Gastro-resistant granules
Liquid preparations for oral use (Praeparationes liquidae peroraliae)	Oral solutions, emulsions and suspensions Powders and granules for oral solutions and suspensions Oral drops Powders for oral drops Syrups Powders and granules for syrups
Oromucosal preparations (Praeparationes buccales)	Gargles Mouthwashes Gingival solutions Oromucosal solutions and oromucosal suspensions Semi-solid oromucosal preparations Oromucosal drops, oromucosal sprays and sublingual sprays Lozenges and pastilles Compressed lozenges Sublingual tablets and buccal tablets Oromucosal capsules Mucoadhesive preparations Orodispersible films
Powders, oral (Pulveres perorales)	Effervescent powders
Tablets (Compressi)	Uncoated tablets Coated tablets Gastro-resistant tablets Modified-release tablets Effervescent tablets Soluble tablets Dispersible tablets Orodispersible tablets Chewable tablets Oral lyophilizates

Production technologies used for preparation of ODTs

A wide variety of methods are used for production of ODTs. The most common and convenient technique used is the classical direct compression method. However, other production methods could be also used, such as moulding, melt granulation, phase-transition process, sublimation, freeze-drying, effervescent method etc.

The choice of the most appropriate method depends on a series of factors, such as the properties of the API, the excipients used in the formulation and their concentration, which factors can significantly influence parameters such as hardness, friability, wetting time, moisture uptake, disintegration and drug dissolution time (Dey and Maiti, 2010).

Direct compression method for preparation of ODTs

Direct compression is a method involving the simplest technology by using conventional tableting equipment, thus it is commonly used for production of ODTs. Tablets formulated in this way are usually characterized by good mechanical properties such as hardness and friability (Brniak et al., 2013). In order to prepare ODTs formulation of desired API, selection of proper excipients is an important factor. To prepare rapidly disintegrating tablets, usually microcrystalline cellulose and low substituted hydroxypropyl cellulose are used. By adding effervescent material, rapid disintegration could be achieved, produced by formed carbon dioxide, which also influences the taste of the tablets. However, control of the hygroscopicity is main challenge when using effervescent materials. Super disintegrants such as sodium starch glycolate, crospovidone, alginic acid, calcium silicate and croscarmellose could be used for fast disintegration, they absorb water, start swelling and improve disintegration of tablet.

Direct compression method is a cost-effective method, and mainly challenge of this process is using disintegrants that can affect tablet hardness (Hannan et al., 2016). In the study in 2017, Gulsun et al. prepared formulation for ODTs of furosemide, by direct compression method, adding microcrystalline cellulose, hydroxypropyl cellulose, aspartame and sodium stearyl fumarate. Prepared tablets showed good compressibility, disintegration time within the European Pharmacopoeia requirements, low weight variation, low friability, acceptable range of wetting time, good dissolution and permeability of API (Gulsun et al., 2017).

In 2017, Tawfeek et al. used direct compression method to prepare ODTs for enalapril maleate, combining enalapril with various super disintegrants. The excipients used were Avicel® PH 101 as a diluent, aspartame as a sweetener and cherry flavour as a flavouring agent. The super disintegrants used were croscarmellose sodium, lycatab, glycols, glycols low pH, glycols low viscosity (glycols LV) and crospovidone at 10% w/w concentration. The ODTs were evaluated for physical properties including drug content, hardness, friability, disintegration time, wetting time and drug release. The antihypertensive effect of the ODTs was followed in rats and compared with a commercial formulation, showed reduction of blood pressure within 1 h (Tawfeek et al., 2017).

Moulding method for preparation of ODTs

Moulding is a convenient method for production of ODTs. Generally, moulded tablets are solid dispersions and have acceptable taste since the matrix is usually produced by water soluble sugars. Moulded tablets are generally produced by blending powder with a hydroalcoholic solvent, then pressed in mould plate to form a mass, and then the mass is removed from mould by air drying. The resulting ODTs are less compact than compressed tablets and have a porous structure.

Moulding can be done by heat process; by using agar solution as a binder and a blister packaging. In general, the API is suspended in the blister packaging; the agar is solidified to form a jelly and it is dried under vacuum at -30 ^{O}C. By no-vacuum lyophilisation, solvent is evaporated from drug solution at standard pressure. All ingredients gum, carbohydrate and solvent are shaped into the mould, the solvent is evaporated. Moulded tablets are low on mechanical strength, which could be a challenge during handling and opening of blister packs (Ghosh et al., 2011).

In the study from 2021, ODTs with dapoxetine were formulated and the effects of the polymer and starch on tablet properties were investigated. They used tree polymers (hydroxypropyl methyl cellulose (HPMC), Carbopol 934P and Eudragit® EPO) and wheat starch as matrix forming materials. The dispersion was casted into a mould and kept in a freezer at -20 °C for 4 h, before being freeze dried for 12 h. Increasing HPMC and Carbopol 934P concentrations resulted in tablets with higher hardness and longer disintegration time, and HPMC was superior compared to Carbopol 934. On the other hand, the usage of Eudragit® EPO did not result in the formation of tablets with satisfactory hardness. HPMC had a stronger effect on tablet hardness in comparison to Carbopol 934P. Incorporation of wheat starch as a binder additionally affected the hardness of ODTs and prolonged the disintegration time (Liew and Peh, 2021).

Melt granulation method for preparation of ODTs

In the melt granulation method superpolystates are the most commonly used excipients with a double role, i.e. as a binder that increases the physical resistance of the tablets and as a disintegrant, which improves the melting of the ODTs in the mouth and solubilizes the particles in the mouth leaving no residues. Syperpolystates have a melting point at 33-37 °C and Hydrophilic Lipophilic Balance (HLB) value of 9. Firstly, they were used in preparation of paracetamol fast dissolving tablets together with mannitol and croscarmellose sodium.

Table 1. API used in production of ODTs dosage forms

Category of API	Used API in ODTs	Ref.
Analgesic	Piroxicam	Panzade et al. (2017)
Anti-inflammatory agents	Ibuprofen	Sugár et al. (2019)
	Ketoprofen	Oliveira et al. (2020)
	Sulindac	Bhavna et al. (2022)
	Phenylbutazone	Waters et al. (2018)
	Naproxen	Hussain et al. (2020)
	Indomethacin	Singh et al. (2008)
	Mefenamic acid	Alshehri et al. (2015)
Antiepileptics	Carbamazepine	Conceição et al. (2020)
	Methsuximide	Roshan et al. (2021)
	Phenytoin	Panraksa et al. (2020)
	Primidone	Zuccari et al. (2022)
	Phenobarnitone	Sznitowska et al. (2005)
	Valproic acid	Bitter et al. (2010)
	Phensuximide	Roshan et al. (2021)
	Oxcarbazepine	Hu et al. (2023)
Antifungal agents	Clotrimazole or Amphotericin B	Serrano et al. (2019)
	Griseofulvin	Gupta et al. (2022)
	Ketoconazole	Dhakal et al. (2022)
	Miconazole	Benavent et al. (2021)
	Nystatin	Marzo et al. (2016)
	Terbinafin	Pyteraf et al. (2023)
	Fluconazole	
Antimalarial	Chloroquine	Gupta et al. (2021)
	Mefloquine	Kaur et al. (2020)
	Proguanil	Tan et al. (2020)
	Pyrimethamine	Sachin et al. (2021)
Antigout agents	Allopurinol	Kaur et al. (2020)
	Probenecid	Tan et al. (2020)
	Sulphinpyrazone	Sachin et al. (2021)
Antihypertensive agents	Amlodipine	Sheraz et al. (2016)
	Diltiazem	Latif et al. (2022)
	Valsartan	Ibrahim et al. (2010)
	Nifedipine	Ozon et al. (2022)
	Diazoxide	Visser et al. (2020)
	Prazosin	Musuc et al. (2021)
	Terazosin	Özakar et al. (2023)

Antibacterial agents	Clarithromycin	Lopez et al. (2015)
	Ciprofloxacin	Guillot et al. (2021)
	Nalidixic acid	Kumari et al. (2023)
	Rifampicin	Matawo et al. (2020)
	Erythromycin	Sahu et al. (2014)
Antineoplastic agents	Chlorambucil	Badawi et al. (2022)
	Methotrexate	Fouad et al. (2020)
	Cyclosporine	Zidan et al. (2015)
Diuretics	Acetazolamide	Parrish et al. (2022)
	Amiloride	Li et al. (2020)
	Chlorthalidone	Park et al. (2020)
	Spironnolactone	Ning et al. (2021)
	Furosemide	Ibrahim et al. (2017)
Antiparkinsonic agents	Bromcryptine mesylate	Vlad et al. (2023)
	Piribedil	Rascol et al. (2010)
Anxolitic	Alprazolam	San et al. (2008)
Sedatives	Chlordiazepoxide	Waqar et al. (2023)
Hypnotic	Meprobamat	Polishchuk et al. (2021)
Neuroleptics	Lorazepam	Boddu et al. (2020) C7761129.
Lipide regulating agents	Gemfibrozil	Konstantinidis et al. (2020)
	Fenofibrate	Kevadiya et al. (2018)
	Clofibrate	Kinani et al. (2022)
	Probucol	Morsi et al. (2017)
Opioid analgesics	Methadone	Lam et al. (2020)
	Diamorphine	Jamieson et al. (2021)
	Pentazocine	Celador et al. (2022)
	Nalbuphine	Arabi et al. (2020)
	Morphine	Atrux-Tallau et al. (2022)
Corticosteroids	Prednisolone, Methylprednisolone	Brniak et al. (2015)
	Hydrocortisone	Haslund-Krog et al. (2019)
	Betamethasone	Timotijević et al. (2022)
	Prednisone	Tawfik et al. (2021)
	Dexamethasone	Soroush et al. (2018)
Oral vaccines	Polio	Tian et al. (2020)
	Tetanus	Bajrovic et al. (2020)
	Diphtheria	Sharma et al. (2008)
	Hepatitis	Ferlak et al. (2023)
	Rubella	Helmy et al. (2022)
	Rabies	
Local anaesthetics	Lidocaine	Göbel et al. (2022)

Nutritional agents	Vitamin A, Beta carotene, D, K, E.	Cupone et al. (2020)
Stimulants	Amphetamine	Ghourichay et al. (2021)
	Fenfluramine	Varnäs et al. (2013)
	Dexampheamine	
Sex hormones	Oestradiol	Kedia et al. (2020)
	Testosterone & Methyltestosterone	Belica-Pacha et al. (2021)
	Ethinyloestradiol	Darwich et al. (2012)
	Norgestrel	Cano-Vega et al. (2023)
	Progesterone	Boelaert et al. (2013)
		Liu et al. (2023).
Antithyroid agents	Carbimazole	Boelaert et al. (2013)
	Propylthiouracil	Liu et al. (2023)

Abdelbary et al. (2004) used melt granulation method to prepare an ODTs of paracetamol. Granules were prepared in a high-speed blade mixer, equipped with a heated jacket. Granulation temperature was 42±2 °C throughout the procedure. The mixture of powders was blended for 3 min at 330 rpm, then the appropriate quantity of superpolystate was added and the mixing phase was continued for 10 min at 480 rpm. At the end the granules were cooled, at room temperature, by spreading them out in thin layers on trays. They proved that the utilisation of a superpolystate is an innovating and viable mean in the preparation of ODTs, as it enables an increase in the physical resistance without exceeding the disintegration time limitations, specified by European Pharmacopoeia.

Phase-transition method for preparation of ODTs

In the phase-transition method ODTs are produced by mixing and compressing the mixture containing two sugar alcohols one with a high melting point and another with a low melting point and heating them to a temperature between their melting points making the tablets harden due to the amplification of interparticle bonds induced by the phase transition of lower melting point sugar alcohols.

Study from 2007, showed that combination of two saccharides and heating are crucial in this production process. Hardness of the tablets after the heating is a result of increasing the inter-particle bonds or bonding surface area in tablets (Kuno et al., 2007).

In the recent study from 2020, an ODTs of lornoxicam was created by phase-transition method, with phase-transition of two sugar alcohols: a. mannitol (melting point 166-168 °C) and xylitol (melting point 93-9 5 °C) or b. lactose (melting point 201.6-203.3 °C) and xylitol. The sugar alcohols were mixed in a bottle for 3 min, with the concentration of the low melting point sugar alcohol in the mixture being set at 5% and compressed. The obtained tablets were coated and dried in oven at heat 97 °C for 30 min. The dissolution rate for the prepared formula was enhanced, hardness, drug content, disintegration time and dissolution were in optimal range, all results successfully confirmed the potential of the prepared ODTs over the conventional tablets of lornoxicam (Abdelmonem et al., 2020).

Sublimation method for preparation of ODTs

In this method volatile ingredients are used, which after the sublimation process produce a porous matrix. Ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride are ingredients that are compressed with the other excipients into a tablet. The volatile material created with these ingredients is then removed from the tablet with sublimation, leaving a porous matrix. Disintegration time achieved of tablets produced by this method was 10-20 seconds. The sublimation process of camphor happens in a vacuum at 80 °C for 30 minutes after preparation of the tablets (Aakash and Mahale, 2022).

ODTs with quetiapine fumarate was formulated by using the sublimation method in a study. The aim was to create an ODTs that will disintegrate in a few seconds. First, the concentrations of super disintegrant, subliming agent and other excipients were optimised in the formulation. Indion 414 was used as super disintegrant, sucralose was used as sweeting agent, mannitol as a diluent and camphor as subliming agent. The tablets were evaluated for thickness, weight variation, hardness, friability, content uniformity, wetting time, porosity, *in vitro* disintegration and *in vivo* drug release. The directly compressible ODTs of quetiapine fumarate with lower friability, greater drug release and shorter disintegration time were obtained using Indion 414 and camphor at optimum concentrations (Kalyankar et al., 2015).

Freeze-drying method in preparation of ODTs

In the pharmaceutical industry freeze drying is a process for production of lyophilizates, biopharmaceutical products and some other specific forms. ODTs created by freeze drying process are with high porosity, light texture, quick disintegration, and low mechanical strength. Freeze drying process is performed in three phases: drug solution/suspension, primary drying and secondary drying, and all processes participate in creating the final pharmaceutical form (Iurian et al., 2016).

Jones et al. (2011) used freeze drying method to formulate ibuprofen ODTs. They explored how physicochemical properties of gelatine, as pH and ionic strength of the formulation, can influence on the ODTs characteristics, as glass transition temperature, wettability, porosity, mechanical properties, disintegration time, morphology of the internal structure of the freeze-dried tablets and drug dissolution. The results from the study revealed that adjusting the pH of the formulation away from the isoelectric point of gelatine, resulted in an improvement in tablet disintegration time, the inclusion of sodium chloride influenced tablet porosity, tablet morphology and the glass transition temperature of the formulations, milling the excipients influenced formulation characteristics, mostly on wettability and powder porosity.

Spray-drying method in preparation of ODTs

During this process, a liquid mixture of material is sprayed into a hot chamber to obtain a highly porous structure. Then, these microgranules are mixed with mannitol and kneaded with distilled water before drying at 60 °C for 2 h. Prepared granules are sieved and blended with other excipients and finally compressed into tablets using the compaction method. Tablets prepared by this method possess high porosity and disintegrate rapidly in the mouth (Ghourichay et al., 2021).

Pooja et al. (2013) prepared ODTs using spray-drying technique, creating aqueous composition matrix, which contain support matrix and other components. The technique is based on a particulate support matrix, which is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. Then is mixed with active ingredients and compressed into tablets. The formulations are incorporated by hydrolysed and non-hydrolysed gelatines as supporting agents, mannitol as bulking agent, sodium starch glycolate or croscarmellose sodium as disintegrating and an acidic material (e.g. citric acid) and / or alkali material (e.g. sodium bicarbonate) to enhance disintegration and dissolution. Formulated tablets were evaluated for hardness, friability, *in vitro* disintegration time and *in vitro* drug release. Granules obtained by the spray drying technique were found to be more spherical which improved flow properties and was supported by scanning electron microscope studies. Inclusion of co-processed excipient base in formulation of ODTs enhanced disintegration significantly. Prepared tablets disintegrated within 20 seconds in aqueous medium.

ODTs of valdecoxib and metoclopramide was created by using the spray drying method in a study. Super disintegrants were used (Ac-Di-Sol, Kollidon CL, sodium starch glycolate), diluent (mannitol) along with sweetening agent (aspartame) in the formulation of tablets. The tablets were evaluated for hardness, friability, water absorption ratio, disintegration time (DT) and *in vitro* drug release. The ODTs prepared by spray-drying were compared with direct compression prepared ODTs, the findings of the evaluation suggested the superiority of the ODTs prepared by spray dried technique (Mishra et al., 2006).

Effervescent method for preparation of ODTs

When preparing the ODTs by using effervescent method mixing sodium bicarbonate and tartaric acid in concentration of 12% (*w/w*) is a basic principle in the entire process. Also, in formulation super disintegrants are added i.e. pregelatinized starch, sodium starch glycolate, crospovidone, and croscarmellose. Sodium bicarbonate and tartaric acid are heated at 80 °C to remove moisture and thoroughly mixed with other excipients, then blends are compressed. ODTs produced in this manner provide enhanced patients compliance (Swamy et al., 2009).

An ODTs with the effervescent method containing glibenclamide was prepared in a study. Main objective of the study was to develop an ODTs of glibenclamide based on highly plastic granules that can be compressed at low pressure to form fast-melting pharmaceutical tablets. Various acid and carbonate sources were studied for the effervescent system. Citric acid was coated with plastic materials such as polyethylene glycol (PEG), sodium bicarbonate was blended with sugar alcohol like mannitol, which gave a physical barrier and protective coating. PEG with its inherent hygroscopic nature could decrease the affinity for moisture of effervescent mixture. Sodium bicarbonate blended with mannitol would give a protective coating. PEG melts at body temperature and does not delay the reaction of acid source and base. The formulation using citric acid-sodium bicarbonate and citric acid-sodium glycine carbonate tablet with PEG and mannitol was found to have better reaction properties and reaction stability than other combinations (Jacob and Shirwaikar, 2009).

Limitations in the process of production of ODTs

The manufacturing processes of ODTs faces many limitations. Due to tablet size, low weight and thin form only a small API dose could be incorporated into the tablet. Therefore, only highly potent API could be used when developing ODTs. However, some pharmaceutical companies have developed oral films, which have more than 50% of drug substance capacity per film weight (ex. GAS-X Strips®) (Borges, 2015).

The development of the new thin strip formulation for

gas relief was the result of the expansion of the "edible film" drug product design that many drug manufacturers are turning to breathe new life into existing products. In this design, the active drug ingredient was pressed into a thin strip of film that melts in the mouth (Daphne, 2007).

Other disadvantages as bitter taste of the tablets and hygroscopicity are issues that vary in the drug development process and need to be taken into consideration when developing an ODTs. Factors such as buccal pH and knowledge of stability of the API in all parts of the GIT should be also taken into consideration in preparation process.

Capacity of API loading

When developing ODTs, some of the primary issues that need to be taken into consideration is API loading capacity. ODTs with film created from hydroxypropyl methylcellulose and casting solvent was prepared and showed outstanding drug loading capacity and faster API release (Steiner et al., 2019). The API loading capacity could be increased by increasing the size and thickness of the tablet, but it might influence patients' compliance, because of thick and brittle film. Increasing the amount of API, will influence the disintegration time, thickness and mechanical properties of the tablet, also it might lead to recrystallization of the amorphous API, affecting the physical properties of the product.

Takeuchi Y. et al. (2018) evaluated an ODTs without API and ODTs with different API loadings: ibuprofen (IBP), acetaminophen, or ascorbic acid. They found that disintegration time of hydroxypropyl cellulose (HPC) films increased in proportion to the film thickness. The addition of API affected the mechanical properties of the ODTs. API loading decreased the tensile strength and elastic modulus. The disintegration time of the films was particularly delayed by the loading of IBP, which was the most hydrophobic drug evaluated in this study. The greatest improvement in the disintegration time of HPC film loaded with IBP was realized by the addition of calcium carbonate, which maintained a suitable tensile strength.

In another study, micronized loratadine particles caused dose-dependent changes in the viscosity of the casting mass and affected the quality of the ODTs. By using an hydroxypropyl methylcellulose matrix, it was possible to obtain a high load of a poorly water-soluble drug with an adequate uniformity of the content while maintaining an *in vitro* disintegration time below 100s (Centkowska et al., 2020)

In a recent study from 2020, ion-pair technology was used for high drug loading in ODTs. Ibuprofen-ethanolamine ion-pair improved the drug solubility in polymer up to 60% (w/w) and physical stability by 30% more than ibuprofen film tablet, and the dissolution rate increased. (Liu et al., 2020).

The other study showed that application of bi-layered ODTs as a medium for API dose dependant reduction of the viscosity may lead to increasing drug loading problems, in the study enalapril was combined in hydroxypropyl cellulose and Hypromellose combination, and higher load of API was achieved (Carolina Visser et al., 2017)

Elbi J. et al. (2020) used novel 3D printing technology as a solution of drug loading capacity problems. They developed 3D printed multi-layered ODTs with benzydamine hydrochloride and proved that the control of the API is possible by changing thickness of the film.

Taste of the ODTs

Finally, ODTs are intended to be used in the mouth. In short time after application, they dissolve and release the API, so the taste in the mouth when using ODTs is an important challenge for every pharmaceutical developer. Variety of methods and technologies are developed to help in masking bitter taste of the API, from the simple addition of flavours and sweeteners to drug complexation with ion exchange resins (Ryeong et al., 2022) or cyclodextrins (Liu et al., 2019).

A complex of donepezil hydrochloride/cyclodextrin was incorporated into an ODTs using HPMC and glycerol in a study in 2019. The prepared ODTs successfully masked the smell and provided fast dissolving (Liu et al., 2019).

Khan Q. et al. (2020) investigated the effects of complexation of fluoxetine with β-cyclodextrins which led to taste-masking effect. They also used cefixime trihydrate and β-cyclodextrin complex which masked the taste and improved dissolution.

Other researchers developed rupatadine fumarate ODTs with ethyl cellulose as hydrophobic polymer and taste masking agent, which successfully resolved the taste issue (Olechno et al., 2022).

Multi-layered fast dissolving ODTs was created with 3D printing method and studied in 2018. Taste masking layer was used to separate from drug layer. On one printer head taste masking layer was printed, on the other print head drug containing layer was printed (Ehtezazi et al. 2018).

Salivary washout effect had influence on sublingual delivery, that's because mucoadhesive polymers as chitosan are added to the formulation to limit short mucosal retention time, was concluded in the study conducted by Kraan et al. (2014).

Influence of the humidity on ODTs

Prepared ODTs are not stable in the environment with high humidity. Special precaution measurements need to be taken in the process of preparing, but also in the process of packaging and final storage of the ODTs. Also, bioavailability of the API must be taken into consideration because high humidity in the environment could start the process of conversion of API. To overcome this issue variety of ODTs forms are researched and designed.

An ODTs with olanzapine was created in a study of Selmin, F. et al. by using hot-melt ram extrusion printing, which limited exposure of olanzapine to water and temperature. Prepared formulation, which consisted of olanzapine loaded ODTs, with maltodextrins, glycerol, water and Span 80 was stable after preparation for over 30 months (Selmin et al., 2021).

In other study, Borges et al. (2017) proposed that residual moisture contents should be in a range of 3-6%, as best practice for various commercial ODTs forms.

Higher amount of humidity can lead to instability of API, because high humidity conditions produced higher molecular mobility leading to crystallization of API or alteration of its crystalline form (Sood et al., 2014).

Janigova N. et al. (2022) conducted study where they evaluated the influence of different drying times on the properties of ODTs, prepared in two semisolid 3D printing setups. In the first experiment, drying times were dependent on the overall print time of each batch. In the second setup, the drying time was set equal according to the longest one. The evaluated parameters were weight uniformity, thickness, moisture content, surface pH, disintegration time, hardness, and tensile strength. Upon statistical comparison, significant differences in the moisture content were found, subsequently affecting the disintegration time. In conclusion, a mutual comparison of the manufactured ODTs showed that the drying time affects their physical and mechanical properties.

Manufacturing Method Limitations

Choosing the right method of manufacturing an ODTs has a lot of challenges. Literature data suggests that there are a variety of methods for preparation of ODTs, each one of them having its advantages and disadvantages. Availability of manufacturing technique and knowledge of the characteristics of API can help in choosing adequate manufacturing technique when preparing an ODTs. Here are some examples of factors that need to be taken into consideration when choosing which manufacturing technique to use.

Temperature sensitive API could not be processed using hot-melt extrusion technique, 3D printing and electrostatic spray deposition method due to the high temperatures used during those processes, which could influence the API stability. Electrospinning technique requires the use of organic solvents, which is not environmentally friendly and solvent residuals should be evaluated. In solvent casting method due to humidity, polymorphic transitions could be induced (Bhujbal et al., 2021). Some other issues in solvent casting may be air bubbles, inappropriate viscosity, film shrinkage and rippling effect.

Zayed et al. (2020) developed domperidone based ODTs with polyvinyl pyrrolidone (PVP) and found that different formulations of film impact on physical and mechanical properties, thickness, resistance, which interfere with drug release rates.

3D printing and inkjet printing methods were not suitable for industrial production, and usually they were preferred for production of personalised medicinal products. Having in mind that these techniques could reduce manufacturing time compared to hot-melt extrusion or solvent casting, inkjet printing techniques could be a choice for thermosensitive API. Still shortage of available printing inks that are suitable for drugs and excipients could be challenging issue for these techniques (Gupta et al. 2021).

Patented technologies for ODTs

A lot of pharmaceutical companies have worked and researched on technologies for production of ODTs. Some of them have patented their finding, to return their investments in research process.

Below are some of the patented ODTs technologies with their interesting findings. Additionally, these technologies help pharmaceutical companies to extend the life cycle of their products, to differentiate them in the marketplace and to improve the process of return of investment in the research. The technologies for the formulation, production, and packaging of the ODTs are covered by several patents as indicated below.

Flashdose (Biovail)

Biovail Corp. launched Nurofen Meltlet, ODTs product with ibuprofen that melts in mouth. Matrix of these tablets was prepared by flash heat processing, consist of self-binding shear. Flashdose technology follows up previously produced Soft Chew and EZ Chew, but these previous formulations needed chewing to release the API. The technology called “flash doses” produces dosage units which readily dissolve in the consumer's mouth, tabletting compositions using this concept have been patented by the inventors. Dosage units produced using “flash-dose” technology have better patient compliance than others because they dissolve easily.

However, “flash-dose” tablet mixes, prior to formation into tablets, are often difficult to handle. The mixes are partially amorphous with high cohesivity, so that they often are sticky and flow poorly in tableting devices. They tend to yield processing problems such as “bridging,” “arching” and “ratholing.” Upgrade of the patented technology modified the cohesive and adhesive nature of “flash-dose” mixes and reduce the stickiness which leads to arching, ratholing and other processing problems (Richard, 1997). With the unique mechanism floss-like crystalline structure is produced, which incorporates active substance, then it is compressed into a tablet, as it is presented in the figure below. Tablets have high surface area for dissolution, which improves disintegration and dissolution. Researchers studied influence of the temperature on formation of structures and concluded that temperature variations could produce instead of floss-like material, small spheres (Pavithra et al., 2019).

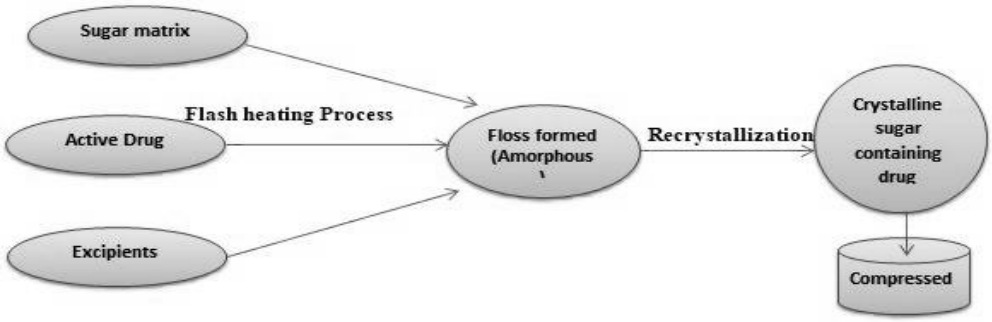

Fig. 1. Schematic flowchart of the Flashdose patented technology for production of ODTs (Source: Fast dissolving tablets. https://jddtonline.info/index.php/jddt/article/view/2292).

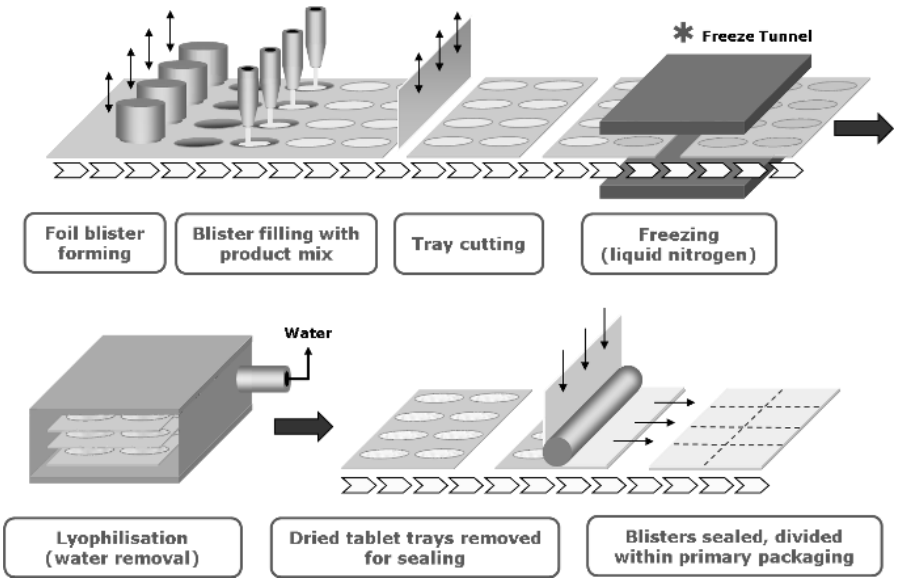

Fig. *2*. Schematic interpretation of Zydis® ODTs patented manufacturing process. (source: Orally Disintegrating Tablets - Catalent, https://www.catalent.com/oral-dose/oral-technologies/orally-disintegrating-tablets/).

Catalent INC. patented Zydis® ODTs, a fast-dissolve formulation, which is unique, freeze-dried oral solid dosage form that disperses almost instantly in the mouth – no water required. (Catalent, 2023). Cyclodextrins and ion exchange resins have been studied for the ability to taste-mask cetirizine HCl when formulated in a freeze-dried oral formulation. A pre-formed resinate of cetirizine HCl and various cyclodextrins was incorporated into the Zydis® oral lyophilizate. In studies which included a human taste trial, 80% of volunteers reported that the formulation that was taste masked using beta-cyclodextrin and cherry/sucralose flavour system was acceptable. Taste masking of the extremely bitter and metallic-tasting drug phencynonate hydrochloride was studied using novel ion-exchange resins. Drug–resin complexes were prepared and characterized, following which the taste-masking effect was evaluated in healthy volunteers of ODTs prepared using the complexes (Chinwala, 2020).

Wowtab (Yamanochi, Astellas)

Astellas Pharma patented the invention of WOWTAB, for production of ODTs, where WOW means "Without Water". In the process of production of these ODTs two different types of saccharides were combined, saccharides with high moldability (maltose, mannitol, sorbitol and oligosaccharides) were combined with low moldability saccharides (lactose, glucose, mannitol, xylitol). Combination of these saccharides resulted in tablets with fast dissolution rate and adequate hardness, and improved stability (Siddiqui, 2010).

Uchida S. et al. conducted study with the aim to determine the amount of water required for ingesting an ODTs of solifenacin (Vesicare®) and Vesicare conventional tablets, they measured the disintegration time of the ODTs in the oral cavity. The clinical disintegration time did not change significantly after unit-dose packaging

or subsequent storage for 56 days. This study showed that the amount of water required for ingesting ODTs is lower than that for ingesting conventional tablets (Uchida et al., 2013)

Frosta (Akina Pharma)

Akina Pharma created an ODTs by using process in creation of plastic granules compressed at low pressure, to gain product with high porosity. These products contain water penetration enhancer, binder and porous plastic material, which provides disintegration time in range of 15 – 30 seconds (Anupam, 2016).

Even though the Frosta® (Akina) technology is not the first FMT technology developed based on the compression method, it is unique because it combines two contradicting properties into one formulation: fast disintegration and high mechanical strength. This technology is based on the compression of highly plastic granules at low pressures to prepare ODTs. The highly plastic granules are composed of three components: a plastic material, a water-penetration enhancer and a wet binder. Each of the three components play an essential role in obtaining tablets with higher strength and faster disintegration time than the other FMT. The key benefits of this technology are:

• fast disintegration in the mouth: within 5 – 40 s depending on the tablet size

• low manufacturing cost: the same as making conventional tablets

• simple processing: one-step wet granulation processing

• strong mechanical property: friability < 1%

• multi-tablet packaging: dozens of tablets in one bottle

Several commercially available FMT were investigated using scanning electron microscopy to understand the important properties necessary for making good FMT. On the Fig. 3 is presented scheme of simplified manufacturing process of highly plastic granules and their fast-melting tablets. The main components used are plastic material, a water-penetration enhancer and a binder. It is critical to select suitable excipients for preparing highly plastic granules (Jeong et al., 2005).

Conclusion

ODTs are a novel tablet concept which offers ease of oral administration and benefits. ODTs are designed to allow administration of an oral solid dose form in the absence of water or fluid intake, disintegrating in the saliva within 60 seconds.

Demand for ODTs has increased, because of impact on patients' compliance process. Patients with swallowing problems (dysphagia), increased variety of GIT cancers and other GIT problems increased the need and the research processes for this type of pharmaceutical formulation. ODTs reached popularity among patients of all ages, children, geriatric, then among institutionalised patients, patients with nausea, vomiting, motion sickness etc. ODTs solve a wide variety of problems encountered in drug administration in these specific population groups.

ODTs are prepared with varying technologies, containing different types of matrices which allow incorporation of a variety of drugs, disintegrating agents that allow fast disintegration of the tablets and fast release of API, flavour and taste additives that help in taste masking, and applicable mechanical strength that allow patients manipulation in different environmental conditions.

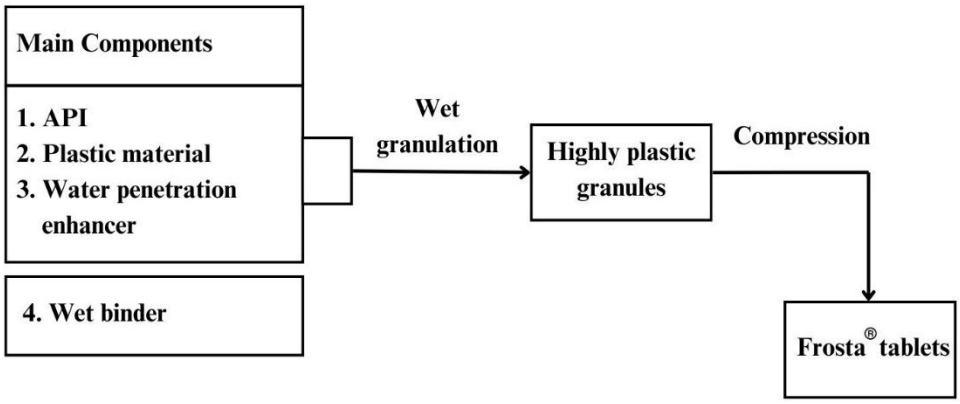

Fig. 3. Scheme of manufacturing process of highly plastic granules and their fast-melting tablets (Frosta® tablets). (adapted from Jeong et al. 2005).

As far as regulatory issues, ODTs are classified as follows:

- United States Pharmacopoeia (USP) approved these dosage forms as ODTs – orodispersible tablets, quick disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets and rapimelts. Food and Drug Administration (FDA) defined ODTs as a solid dosage form with incorporated medical substance or active ingredient that disintegrates within a second after placing upon the tongue.
- European Pharmacopoeia has used the term orodispersible tablet for tablets that disperse readily and within 3 min in mouth before swallowing.

The research is still going on, these technologies use expensive processing, producing fragile tablets that require specialized packaging. Conventional tableting procedures can be used for ODTs but a lot of modifications are required for improving the disintegration time. Using generic API will increase the number of commercialized products, improve patients experience, and enlighten producers' knowledge for such a novel pharmaceutical dosage form.

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Резиме

Технологии на производство и формулациски пристапи при развој на ородисперзибилни таблети (ОДТ)

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Клучни зборови: ородисперзибилни таблети, предности/недостатоци на ODTs, технологии на производство на ODTs, патентирани технологии

Еден од новите начини за доставување на лек, а кој се развива се почесто во последно време се таблетите што се дисперзираат во устата (ODTs), познати како таблети кои се распаѓаат во устата или таблети кои брзо се растворааат. Европската Фармакопеја (Ph. Eur.) ги дефинира (ODTs) како необложени таблети кои се наменети да се стават во устата, каде брзо ќе се распаднат пред да се проголтаат, распаѓајќи се во рок од 3 минути. ODTs имат многу предности како што се: лесно голтање особено за педијатриски, геријатриски или лежечки пациенти, како и за пациенти кои имаат недостаток до пристап на вода за пиење; брзо ја ослободуваат API и имаат брз почеток надејство; зголемена биорасположивост. Повеќето од новите системи за испорака на лекови тешко се прилагодуваат за масовно индустриско производство, па затоа една од многуте придобивки на ODTs е тоа што може да се произведуваат со помош на конвенционална технологија, што ги прави трошок исплатливи. Сите овие придобивки водат кон подобрување на усогласеноста на пациентот кон терапијата. Овој преглед ги разгледува предностите и недостатоците на ODTs, достапните технологии за производство, вклучувајќи ги и патентираните технологии, главните предизвици во формулацијата на ODTs и различните пристапи за нивно решавање и како развиваат истражувањата за ODTs како нов систем за испорака на лекови.