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Review Article

QBD-BASED DEVELOPMENT OF ORODISPERSIBLE FILMS OF ANTIPSYCHOTIC DRUGS

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ABSTRACT

This review provides an overview of the application of the Quality by Design (QbD) approach in the formulation and evaluation of the orodispersible films (ODFs) of antipsychotic drugs. Quality by Design involves a well-defined approach with predefined objectives to develop the product or process based on quality risk management and sound science. It comprises the defining of Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs), risk assessment, design and development, and evaluation of formulation. The Orodispersible films are ultra-thin, elegant, and portable dosage forms that do not require water to be ingested. It can be used for individuals who require special needs, such as for treating psychosis, schizophrenia, mania, and dysphagia. Hence, it holds tremendous potential in terms of patient compliance, convenience, and pharmacotherapy. They are fabricated by different techniques, which include solvent casting, hot-melt extrusion, 3D printing, and others discussed here. They are evaluated for different attributes like mechanical strength, dissolution, disintegration, tensile strength, folding endurance, and others discussed here. It also provides the significance of stability, packaging, shapes, and patent-related concepts of orodispersible films.

Keywords: Quality by Design, Orodispersible films, Antipsychotic drugs

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INTRODUCTION

Recently, the pharmaceutical industry's attention has shifted to Quality by Design, which is a new approach to pharmaceutical development with pre-determined goals. It has evolved into a new paradigm for the production of safe and effective pharmaceutical products. "Systematic approach to development that begins with established objectives and prioritizes product and process understanding and process control, based on strong science and quality risk management," as defined by QbD. As a result, the fundamental principle of QbD is that "quality cannot be tested into a product; rather, it must be built into the product"[1]. Design of Experiments (DOEs) and Process Analytical Technology (PAT) are the 2 most common tools used in QbD. The current framework involves recognizing and establishing a Target Product Profile (TPP), risk assessment, recognizing CQAs of the drug product, and establishing a control strategy for preparation process controls and accurate monitoring of the operation to certify the product quality. As a result, by monitoring the formulation and operation parameters, the QbD assures quality. The advantages of QbD include the minimization of batch failure, fewer regulatory compliance challenges, lesser production costs, and enhanced product understanding [2].

Pharmaceutical companies are currently focusing their research primarily on the development of innovative drug delivery systems, as traditional drug delivery systems such as tablets and capsules have several limitations. The limitations include the necessity for water for disintegration, the possibility of choking, and the fact that it is unideal for infant, geriatric, or coma patients. After the investigation, it was revealed that 26% of 1576 participants had issues with swallowing tablets [3]. The participants with Parkinson's disease, vomiting tendency, oral cancer, and bipolar disorders have swallowing difficulties [4]. Oral Disintegrating Tablets (ODTs) evolved as a solution to this issue, replacing traditional capsules and tablet dosage forms. This dosage form dissolves instantly when placed on the tongue, releasing the medication, which dissolves or disperses in the saliva [5]. When local action in the mouth is desired, such as for toothache, oral ulcers, cold sores, or teething, orally disintegrating tablets can be used, as can those who cannot swallow intact sustained action tablets/capsules [6]. Despite this, ODTs face many difficulties, such as maintaining stability through rigorous dehumidification, taste concealing efforts culminating in the enlargement of size, 'sweet' sensation leading to excessive consumption, choking concerns, and fragility in strength [7].

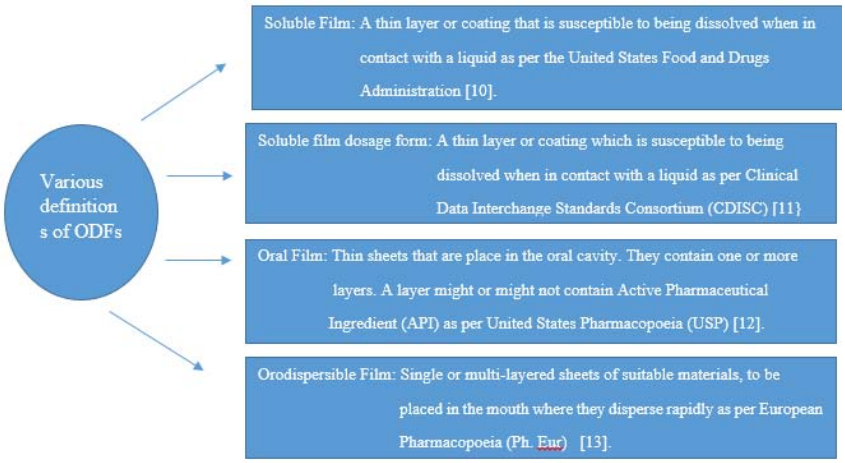


Fig. 1: Various definitions of ODFs

The above-mentioned points strongly recommend that a better pharmaceutical dosage form must eliminate the complications related to swallowing conventional dosage forms by the specific patient populations. In this direction, one such innovative and useful dosage form focused is ODFs. Orodispersible films are defined as stamp-sized paper-thin, attractive and convenient, patient-oriented dosage forms that do not require water consumption. Compared to ODTs, this form of oromucosal preparation has a faster disintegration period in the mouth cavity. The ODFs can be used for treating various conditions like motion sickness and allergic reactions where instant action is required. The ODFs administered through the sublingual and oral route have the opportunity to reduce the dose and enhance the action. ODFs can enhance patient convenience by masking the taste of astringent medicines [8, 9].

ODFs have few limitations. Moisture susceptibility, extreme temperatures, high loading dose issues, APIs that irritate oral mucosa cannot be used and the need for expensive packaging is among the disadvantages of orodispersible films [14, 15].

Dr. L. L. Frederick Deadman initially introduced thin oral dosage formulations at the beginning of the 1960s [16] and they were slowly developed at the end of the 1970s [17]. Pfizer developed the first ODF as an oral refreshing film, popularly known as Listerine PocketPaks [18], which was a non-medicinal product. Following Pfizer's initial impact, plenty of other companies jumped into the ODF field, launching lots of new Over-the-counter (OTC) and prescription medications that are already authorized and commercialized. The first therapeutic ODF was introduced by Prestige brands, namely, Strips containing menthol and benzocaine known as Chloraseptic strips for treating the pain of sore throat [19]. In 2008, the first ODF made up of herbs comprising senna glycosides for treating constipation was launched by C. B. Fleet company [20]. Following that, in 2010, the markets saw ODFs comprising prescription medications for the first instance. Reckitt Benckiser obtained Food and Drugs Administration (FDA) approval for a pain management film containing buprenorphine and naloxone manufactured employing MonoSol's Pharm Film technology [21].

Antipsychotic drugs are defined as drugs used mainly for treating schizophrenia. They are also known as neuroleptics or tranquilizers. These are used for treating psychotic symptoms such as paranoia, grandiosity, hallucinations, and delusions. The antipsychotics are not alleviative but help in reducing the intensity of hallucinations and delusions. They act by blocking the dopaminergic activity in the mesolimbic system of the brain. They were classified into two categories.

1) Typical antipsychotics are also known as first-generation antipsychotics. Some of the examples of this category of drugs include Chlorpromazine, Thioridazine, Fluphenazine, and Haloperidol.

2) Atypical antipsychotics are also known as second-generation antipsychotics. Some of the examples include Aripiprazole, Quetiapine, Olanzapine, and Risperidone [22].

We explored the papers in four English databases, including PubMed, Google Scholar, Elsevier websites, and google patents, of the last fifteen years to find all papers regarding orodispersible films. The initial step of the search included papers written in any language that had an English abstract. "Orodispersible film formulation," "QbD-based drug delivery system development," "Antipsychotic drugs" and "orodispersible formulation composition" were among the terms we used. The studies evaluating the conventional and novel approaches in the formulation and characterization included so far in the formulation, highlighting the elements of QbD involved in the development, formulation, and characterization of orodispersible films, were included in the latest study as inclusion criteria. But the papers with insufficient data, the abstract without full text, in conformity between methods and results, and the inappropriate explanation of the findings were excluded from this review. However, studies with insufficient data, abstracts without complete text, lack of uniformity between techniques and outcomes, and inadequate explanations of findings were eliminated from this review.

Components of QbD

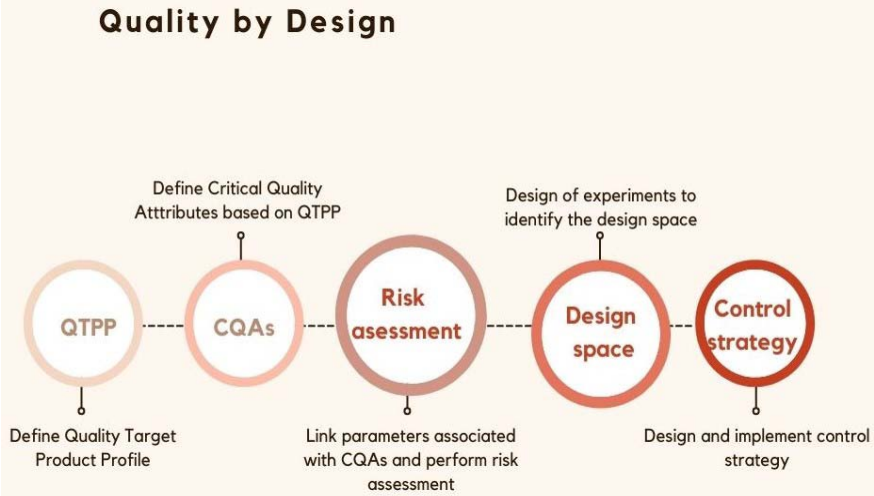


Fig. 2: Components of QbD

Quality target product profile

This is a key component of QbD. QTPP can be defined as a complete product description that summarizes the quality characteristics expected to ensure product performance, stability, safety, and efficacy.

Critical quality attributes

CQAs stands for Critical Quality Attributes. QTPP helps to recognize CQAs. CQAs are defined as "physical, chemical, biological, or microbiological properties or characteristics that should be within suitable limits to guarantee the required quality of the product". The Active Pharmaceutical Ingredient (API), polymers, and other additives used in the manufacturing of an ODF are all related to CQAs. CQAs are determined based on a prospective summary by using the quality attributes. It starts with a cost-benefit analysis of modifying variation in product/process characteristics. The quality characteristic in question is regarded as a critical quality attribute if the altered variable leads to significant harm to the patient.

Table 1: Elements of QTPP of Orodispersible films

S. No.	QTPP element	Target	Justification	References
1	Dosage form	Orodispersible film	Ease of administration	[23]
2	Dosage design	Immediate or sustained release	For desired therapeutic activity	
3	Route of Administration	Oral	Oral administration reduces the risk of systemic side effects	
4	Dosage strength	% w/w	Less dose (Potent drugs)–ideal to develop ODFs	
5	Primary packaging	Necessary to be compatible	Aluminium sachet, plastic box–to protect from moisture, microbial attack and light.	
6	Pharmacokinetics	Necessary to be bio-equivalent	Tmax: Cmax: Area under the curve (AUC): Distribution volume: Plasma protein binding: Major metabolite: Elimination half-life:	
7	Ease of storage and distribution	Necessary to be stable and compact	It must be both stable and compact.	
8	Stability and shelf life	Necessary to have a good shelf life	Stable against microorganisms, ambient moisture, and light.	
9	Patient acceptance and compliance	Aid to achieve compliance and acceptance	➢ Useful for patients with dysphagia. ➢ Taste masked to gain acceptance. ➢ Do not spit the ODF. ➢ Do not chew the ODF. ➢ Directly placed on the tongue and disintegrates quickly ➢ No requirement of water to ingest and hence can be consumed on the go.	

Table 2: Critical quality attributes of orodispersible films with Justification

Quality attributes of drug product	Target	CQAs	Justification	References
	Appearance	No	Color, shape, and appearance do not directly affect safety and efficacy. So, they are uncritical. The target is set to guarantee patient acceptability.	[24]
	Dimension	Yes	It should be of a size that allows it to be placed in the mouth cavity.	
	Peel adhesion	Yes	It is necessary to remove the film from the slab or support with ease	
	Assay	Yes	To ensure that the therapeutic dose and availability are sufficient to have the desired therapeutic effect	
	Disintegration time	Yes	Patient compliance is improved by rapid disintegration. Spitting or choking can happen when rapid disintegration fails.	
	Dissolution profile	Yes	Assists in the interpretation of the drug release rate to prove the desired therapeutic effect	
	Content uniformity	Yes	Assists in maintaining ODF consistency in performance.	
	Water content	Yes	Helps in the detection of microbial attacks and stability	
	Tensile strength	Yes	to make it easier to store and manage ODF for administrative purposes	
	Microbial load	Yes	Assists in the maintenance of stability and safety.	

Risk assessment: to know the linkage between critical material attributes and critical process parameters with critical quality attributes

Risk assessment is the evaluation and control of potential risks in actions undertaken during the manufacturing process [25]. This is a key step in the QbD-based development because the high-risk parameters which can affect the CQAs of ODF are analyzed during this step. The evaluation would aid in establishing which material attributes and process variables are crucial, and it would recommend additional research into those areas to guarantee quality. Process parameters and material attributes critical to assuring the quality of product are called Critical Process Parameters and Critical Material Attributes, respectively.

Critical material attributes

It can be described as the biological, chemical, and physical characteristics of the substances used for the preparation of the formulation. The substances used for the formulation can be active drug substances, liquids, and process aids. The material properties are assessable and must be within the required limits to produce the desired product. S. M. Krull *et al.* have explored several factors of the polymer's impact on ODF drug delivery. They looked at how polymers affected the administration of drugs with low or no water solubility [26]. Furthermore, Krull *et al.* assessed the influence o two plasticizers, namely, Poly Ethylene Glycol (PEG)-400 and glycerol as well as nanoparticles of poorly soluble Griseofulvin as a prototype drug, concerning plasticizer concentration. The plasticizer concentration has a major impact on the mechanical characteristics of the nanosized drug but has very less or no effect on the drug's release profile from ODF, according to this research [27].

Critical process parameter

It is a parameter of the process whose variation influences CQAs and hence it should be maintained to ensure the process gives the required quality. CPPs involved in the solvent casting process of making ODFs were identified by Silva *et al.* Temperature, Relative Humidity (RH) are critical process parameters for producing ODFs with sufficient mechanical characteristics, specified residual water content, and a rate of drug release. The researchers discovered that a room temperature of 20–25 °C, a drying temperature of 60 °C, and a % RH of 30–58%, are all essential for developing ODFs with the optimal release of the drug even after 150 d of storage period [28]. Finally, it provides a design area where process parameters may modulate to produce high-quality ODF.

For developing an ODF from laboratory-scale to continuous manufacturing process, Thabet and colleagues used International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q8 (R2) requirements to construct a Cause and Effect diagram (fig. 3) [29].

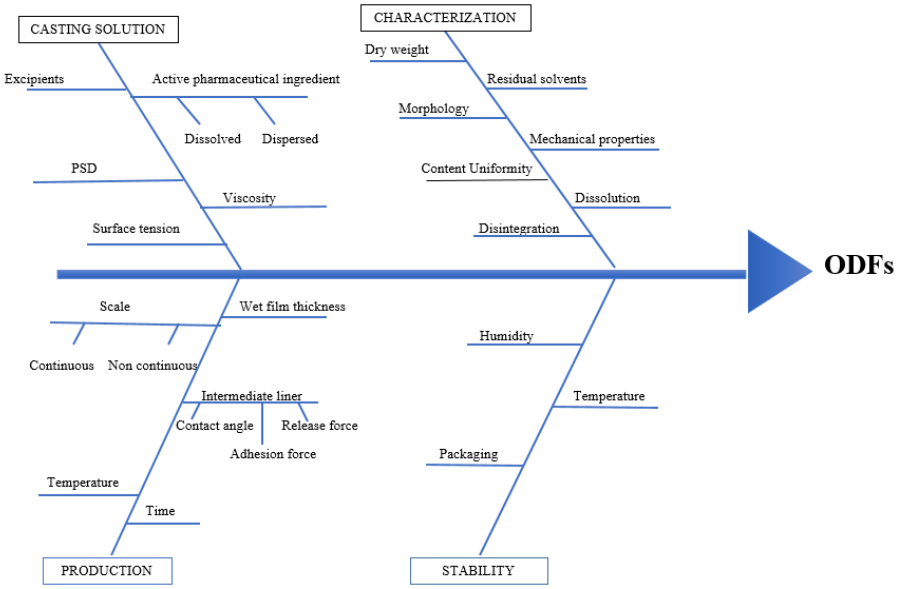


Fig. 3: Cause and effect diagram for the formulation development of orodispersible films Adapted from Ref [30]

The researcher developed a framework to evaluate the risk linked with each material property and processing variable concerning the ODF CQAs.

The main outcomes of this study are explained as follows.

The chemical stability, physical stability, and polymorphism of drug substances have a direct impact on the stability of orodispersible films. The concentration of the polymers and plasticizers used in the formulation mainly influences the important attributes like dissolution, disintegration, content uniformity, and tensile strength of orodispersible films. The parameters monitored during the manufacturing process, like drying temperature and drying time have a direct impact on the stability and tensile strength of the formulation. One of the most significant attributes of the formulation is content uniformity. It can be influenced by the parameters like mixing speed and mixing time, which should be monitored carefully. The order and rate of addition of ingredients have a direct impact on the assay of the active pharmaceutical ingredient used in the formulation.

Design of the experiments

Design of Experiment (DoE) is a statistical tool employed in pharmaceutical product development. It has been proposed that DoE will deliver 4–8 times higher than the value of operating the tests in a relatively short time that this could consider taking a test of a single factor at a time in One Factor At a Time (OFAT) experiments. In the pharmaceutical industry, using DOE helps to obtain the most information from a very less number of experiments [30]. There are mainly two types of design 1) Screening design. It is used to study a wide range of variables with very less runs in experiments. Examples of screening design include fractionating factorial design, Placket-Burman design, and two-level full factorial design. 2) Optimization design. These are used to identify the variables that optimize the response. Examples of optimization design include Box-Behnken design, response surface design, and central composite design. The choice of design of experiment is influenced by the effectiveness of the design, the number of input factors, and other factors. The purpose of the DOEs is to determine the design space.

Design space

It is defined as the demonstrated multidimensional combination and interactions of input factors and process variables for quality assurance. The application proposes it, and it is subject to regulatory evaluation and approval.

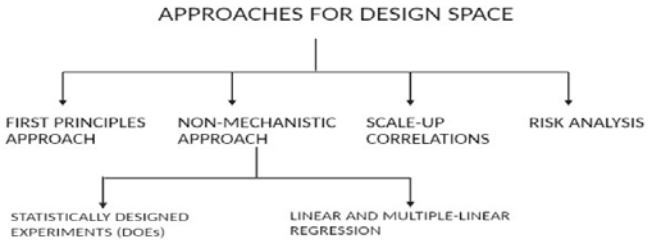


Fig. 4: Different approaches for the determination of design space

To determine the design space, any combination of the above-mentioned approaches can be employed.

Control strategy

It is stated as a designed set of controls that ensure process performance and product quality based on the current process and product knowledge. To ensure product quality, these types of controls should be closely checked. The variables and attributes linked to the components, drug substance, drug product, facility, operating environment, in-process controls, and final product standards are included in the controls.

Composition of orodispersible film formulations

The development of orodispersible films is mainly concerned with the complete application of performance and aesthetic aspects like taste concealing, physical appearance, fast dissolving, mouthfeel, etc. The ingredients involved in the preparation of orodispersible film are mentioned below in categories based on the use. From a

regulatory standpoint, all components used in the manufacture of the orodispersible film should be regarded as safe i.e. Generally Recommended As Standard (GRAS)-listed and allowed for use in oral pharmaceutical formulations.

The ingredients used in the formulation of orodispersible films are active pharmaceutical ingredients, hydrophilic polymers, plasticizers, saliva stimulating agents, sweetening agents, flavouring agents, surfactants, and colouring agents [31-33].

Table 4: Composition of orodispersible film formulations

S. No.	Ingredients	Quantity (%)	References
1	Active pharmaceutical ingredient	1%-30%	[31, 34, 35, 36 and 37]
2	Hydrophilic Polymers	40%-50%	
3	Plasticizers	0%-20%	
4	Saliva stimulating agents	2%-6%	
5	Sweetening agents	2%-6%	
6	Surfactant	q. s	
7	Colouring agents	q. s	
8	Flavouring agents	q. s	

Active pharmaceutical ingredient

To begin with, drug solubility and permeability are important factors in choosing a drug of choice for the production of ODFs. The main candidates used for the preparation of ODFs are BCS Class III and II drugs. The active substance present in the film is at a percentage of 1%-30% w/w. As high doses of drugs are difficult to incorporate into orodispersible films, it is recommended to use a low dose potent active substance for the formulation of ODFs. A micronized API formed by the micronization of an active substance is beneficial since it improves the texture of the surface and dissolution in orodispersible films. As a quick dissolving oral film, various medications can be used [32, 33].

Table 5: Category of drugs with examples used for the formulation of ODFs

Category	Examples	References
Anti-emetics	Dronabinol, Aprepitant, Ondansetron, Metoclopramide and Trimethobenzamide	[36-38, 40]
5 Hydroxy Tryptamine (5HT) 3 blockers	Ramosetron, Granisetron, Ondansetron, and Alosetron	
Anticonvulsants	Carbamazepine, Gabapentin, Lamotrigine and Valproate sodium	
Anti-migraines	Almtriptan, rizatriptan, zolmitriptan and Nartriptan	
Antipsychotics	Haloperidol, Prochlorperazine, Aripiprazole, Quetiapine and Zotepine	
Statins	Atorvastatin, Fluvastatin, Lovastatin, Rosuvastatin and Simvastatin	

Hydrophilic polymers

The polymers mainly used as agents for the formation of the film layer act as the main component in the ODFs preparation. As orodispersible films are placed in the oral cavity for their therapeutic action, hydrophilic polymers are mainly used in the formulation. The water-soluble polymers used are Hydroxy Methyl Propyl Cellulose of different grades like E3, E5, K3, Methyl Cellulose of different grades like A3, A6, A15, pullulan, gelatin, and sodium alginate [31, 32, 35, 38].

Plasticizers

The plasticizer is an essential component in the formulation of orodispersible films. This assists in improving the elongation, flexibility, and tensile strength of the films. It also helps reduce the fragility of the orodispersible film with the inclusion of Plasticizers. The plasticizer opted for will be determined by the solvent type used in the manufacturing process and the plasticizer's suitability with polymer. Some of the examples of plasticizers used in the formulation are Polyethylene glycol, Sorbitol, Glycerol, and Propylene glycol [33, 39, 40, 42].

Saliva stimulating agent

The objective of employing saliva stimulating substances is to speed up the production of saliva, which will aid in the quick disintegration of ODFs. Salivary stimulants are usually acids used in food preparation, such as ascorbic acid, citric acid, lactic acid, and malic acid. These can be used alone or along with a 2 to 6% w/w film concentration [32, 34].

Sweetening agent

Sweeteners are an important component of food and medicinal preparations that are intended to be disintegrated or dissolved in the mouth. Both handmade and natural sweeteners are employed in the preparation to increase the mouthfeel of the ODFs. Sweeteners are typically employed in the preparation at a proportion of 3%-6% w/w, either alone or in the combination of two or more [32, 39, 40].

Table 6: Sweetening agents used in the formulation of ODFs along with their respective sweetness factor

Sweetening agent	Sweetness factor	References
Neotame	7000–13000	[41]
Aspirin	180–200	
Sucralose	600	
Saccharin	300	

Flavouring agents

The flavour chosen is determined by the type of medication to be included in the preparation. A patient's ability to recognize orodispersible films is based on the first flavour character that is noticed in the first few seconds after the product consumption, and the formulation's aftertaste lasts for at least 10 min. The type and strength of the flavour impact the amount of flavour needed to cover the taste. In the product, the flavouring compound is used at a concentration of 10% w/w [35, 40, 41].

Table 7: Type of flavouring agent with its examples used in the formulation of ODFs

Flavouring agents	Examples	References
Salty	Butterscotch, apricot, peach (because anions and cations such as KBr are present)	[43]
Sweet	Vanilla, fruit, berry (Because of the presence of polyhydroxy compounds, polyhalogenated compounds	
Bitter	Wild cherry, mint, and walnut (because they contain free bases such as alkaloids and amides such as amphetamines)	
Sour	Liquorice, raspberry, citrus (because of the presence of hydrogen ions)	

Colouring agents

The orodispersible film contains colouring additives that have been authorized by the Consumer Product Safety Commission and Food and Drug Administration. Generally, the concentration of colouring additive in the orodispersible film does not exceed 1% w/w. The commonly used colouring agent used in the formulation is Titanium dioxide [31, 33, 40].

Methods of preparation of ODFs

In this part, we will look into the most common methods used by research scientists worldwide; they are the solvent casting method, hot-melt extrusion, printing, and electrospinning methods used in different scenarios.

Solvent casting method

The solvent Casting Method is perhaps the most fundamental, commonly employed, and direct method for manufacturing ODFs among the various methods [44-46].

ODFs can be manufactured continuous or as a batch process employing the process by selecting the suitable drying conditions. The temperature at which the ODF is dried is significant as the API degradation and mechanical instability can be caused by high temperatures. Furthermore, the low boiling points of organic solvents and elevated drying temperatures can lead to the production of air bubbles forming in the middle of ODFs, impacting the drug's uniformity [29].

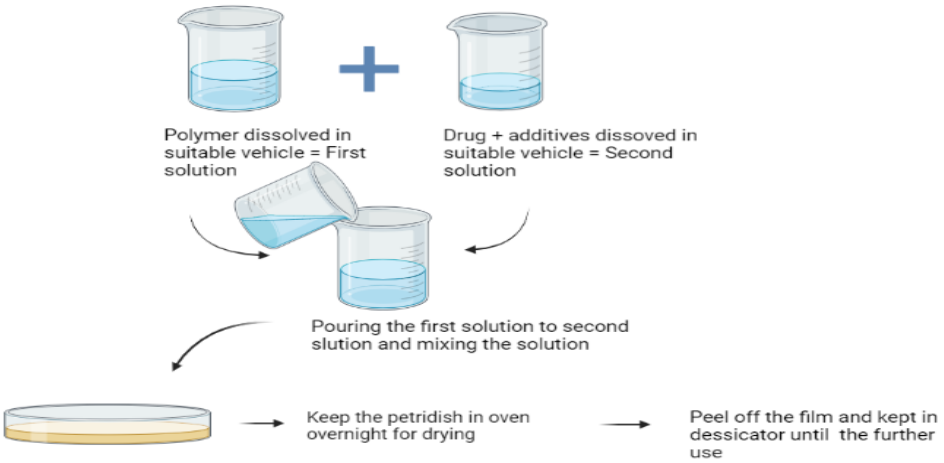


Fig. 6: Steps involved in the solvent casting

The SCS (consisting of carbomer 97 4P and hypromellose) developed by Visser and colleagues in a previous study was used to make double-layered enalapril maleate ODFs. Enalapril lowered the viscosity of SCS by changing the pH and salting-out action. To have to get over these problems, the authors used SCS to make double-layered enalapril maleate ODFs [49].

Electrospinning method (EM)

It is another method used for the fabrication of ODFs based on the utilization of solvents. It is also known as "electrostatic spinning". This method involves two steps.

1) Preparation of electrospinning solution

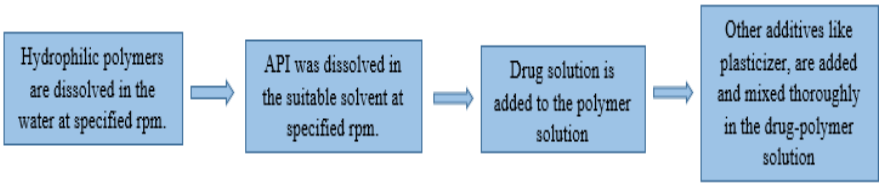


Fig. 7: Steps involved in the preparation of electrospinning solution, the solution formed in this process is called "electrospinning solution"

Fabrication of the films by electrospinning

Design of the apparatus

A syringe with a specified volume is fitted in a syringe pump. Through a tube, an injection needle with a specified internal diameter is connected to the syringe. The positive electrode of a high-voltage power supply was linked to the needle, while the farthing electrode was attached to a revolving metal drum receiver covered in aluminium foil. At room temperature, the process of electrospinning was performed. There was a 10 cm gap between the receiver and needle.

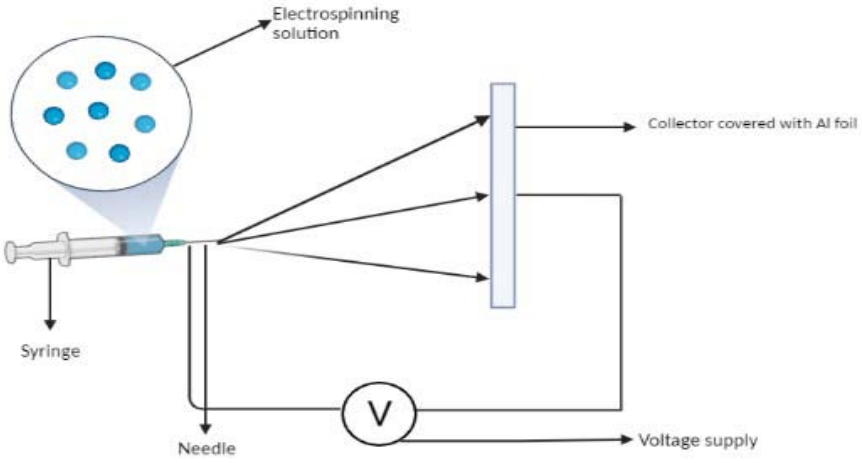


Fig. 8: Steps involved in the electrospinning process (Adapted from Ref. No. 47)

Illangakoon *et al.* used a similar process to make fast-dissolving ODFs from electrospun polyvinyl pyrrolidine (PVP) nanofibers by combining caffeine and paracetamol [51]. When tested with simulated saliva, the films disintegrated completely within 0.5 sec. The drug cargo was delivered in two and half minutes in a dissolving test.

Rustemkyzy *et al.* used Electrospinning Method (EM) to fabricate potassium iodate ODFs that dissolved very rapidly. Potassium iodate and polyethylene oxide were dissolved in water and electrospun to produce a potassium iodate nanocrystal-loaded nanofiber film with good mechanical characteristics and disintegration properties (less than 30 sec). As a low-cost iodine supplement formulation, this product was developed specifically for pediatrics with swallowing difficulties [52].

Luraghi and colleagues published an outstanding review recently that highlighted the concepts behind the electrospinning process and its significance in many pharmaceutical applications [53].

Hot-melt extrusion method

Hot-Melt extrusion (HME), which would not require the usage of liquids like the Solvent Casting Method and EM, is another method for developing ODFs [48]. This approach employs a ram/single screw or multi-crew-based device.

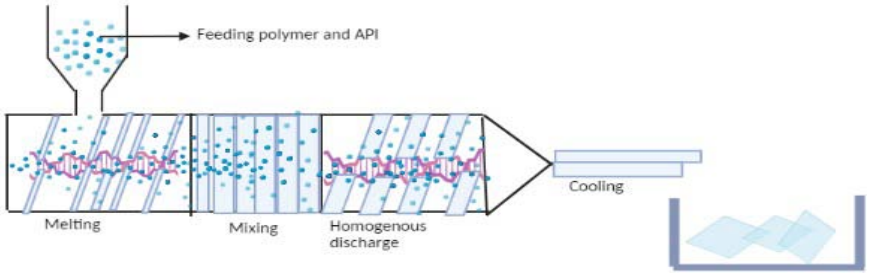


Fig. 9: Hot melt extrusion process

The merits of this method include no solvent usage, minimal steps, a better approach for poorly soluble drugs, and less energy required.

The demerits include thermal deterioration due to high temperatures, flow characteristics of the polymer, few polymers are available and water or any other volatile solvent should be excluded from the preparation [31, 37, 54, 55].

Pimarande and their team developed rapid dissolving ODFs of chlorpheniramine maleate, which take 6–11 seconds to dissolve, using a one-screw-based HME. They used polymers based on starch that was subsequently plasticized with glycerol in this method of manufacturing. The researchers employed a degassing port to obtain a high-quality product while also removing the vapours produced during the procedure [56].

Jani and Patel published an outstanding and comprehensive assessment of Hot-Melt Extrusion (HME) as a method for fabricating ODFs. They discussed excipient selection, numerous industrial extruders, and downstream apparatus in their review. More significantly, they highlighted the common issues encountered during fabrication and provided solutions to the issues. The researchers recognized ingredients, CQAs, QTPP, and CPPs for ODF fabrication by HME [24].

Printing method

The modern method employed for developing ODFs is the printing method [57].

While the above procedure is typically considered a two-dimensional printing method, it can even be used to fabricate ODFs using 3D printing (3DP) procedures. The 3D printing can be done by an instrument called a 3D printer.

The key difference between the subsequent three-dimensional printing methods and the preceding two-dimensional printing technologies is that with 3D printing, Drug substance comprising ink is printed to produce the ODF, whereas, with two-dimensional printing, Drug substance-comprising ink is put onto an established substrate. To fabricate ODFs, three-dimensional printing methods such as semi-solid extrusion 3-dimensional printing [58], hot-melt ram extrusion 3DP [59], and fused deposition modeling [60] could be used.

Khalid and their team recently published solid evidence research on printing taste-concealing ODFs of the temperature-sensitive medication diclofenac sodium using a hot-melt ram extrusion procedure. The finished ODFs were confirmed to be stable even after accelerated stability studies [61].

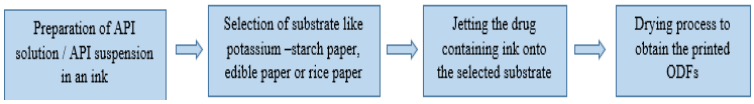


Fig. 10: Steps involved in the printing process of ODFs

Fig. 11: 3D printer instrument

Significance of shapes in the orodispersible films

ODFs are available in a variety of various shapes, namely squares, rectangles [62], and long strips. Niese and colleagues were the first to create long Warfarin Sodium ODFs for personalization and versatility in treatment. The lengthy ODF that was designed might be coiled and cut with a cutter. The film was also determined to be stable over 12 w [63]. LTS Lohmann proposed a U-shaped film for drug delivery to maximize sublingual region use. They have specifically designed many U-shaped ODFs, such as a 'square' U, or a 'pointed square' U and 'round' U that better utilize the 'frenulum linguae' [64]. It's significant to include ODF-based sublingual immunotherapy now.

ODFs were patented by The John Hopkins University (TJHU) for therapy of food and other allergies which were administered by sublingual route [65]. TJHU developed ODFs employing a variety of extracts of allergens, including meat extracts, food extracts, tree nuts, peanuts, and others, according to its patent application. Peanut extract was perhaps the most preferred extract. As a result, sublingual immunotherapy using ODFs has shown to be beneficial in the treatment of food allergies, notably peanut allergies.

Characterization of orodispersible films

The orodispersible films developed are characterized in the following aspects.

Evaluation of physical properties

Visual inspection was used to evaluate the surface, brittleness, transparency, colour, flexibility, and homogeneity of the orodispersible films [66, 67].

Weight variation

Each film is weighed and mean weights are determined to account for weight variation. The mean weight of the films is then subtracted from each film's specific weight. A significant difference in weight indicates that the procedure used was ineffective, and the drug content is likely to be non-uniform. Three films of the desired size are evaluated which are cut from a single film [66, 68].

Thickness

At different important points, the thickness of the film is evaluated using a micrometer screw gauge. This is necessary to ensure consistency in the thickness of the film, as the thickness of the film is specifically related to the dose uniformity in the film [66, 67, 69].

Disintegration studies

The Center for Drug Evaluation and Research (CDER) recommends a disintegration time of 30 sec or less for orally disintegrating tablets. It's suitable for orodispersible films. Although there is no regulatory guidance for oral rapid dissolving films/strips, this could be used as qualitative guidance for product testing procedures or during the design phase. A film's average disintegration time is 5–30 seconds. A film's disintegration time provides information about its dissolution and disintegration properties.

The Petri dish method is the most common technique for evaluating the disintegration time of ODFs.

Petri dish method

In this method, the ODF as per the specified dimension required for drug delivery, is placed on the petri dish comprising potassium buffer solution (pH 6.8). Disintegration time is the amount of time it takes for the film to disintegrate in the buffer. 3 films of every formulation were tested and mean±S. D was computed [31, 66, 68-70].

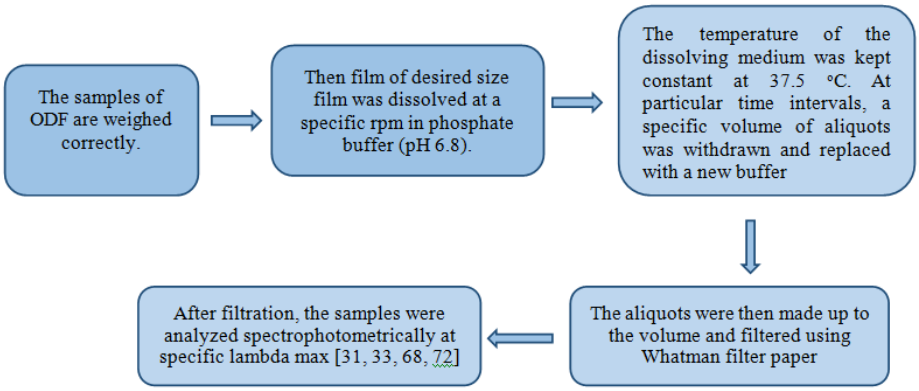
The main demerits of this method include initial and final disintegration times are not well defined, the timer is used manually and the volume of the medium would be required is 20 to 25 ml.

M S Gupta and colleagues devised a new and innovative disintegration evaluation system centered on Light Dependent Resistor (LDR) and Light Emitting Diode (LED) sensor technology, as well as a thorough review of the characterization of ODFs. The disintegration evaluation apparatus operates on the concept of photoconductivity and can reliably measure both the initial and final disintegration times of ODF. The optimal ODF takes less than 30 sec to disintegrate [71].

Dissolution test

Any of the pharmacopeia's regular basket or paddle devices can be used for dissolution testing. The dissolution media would be determined by the sink settings as well as the maximum dose of the drug substance. When the film is moistened, however, it dissolves in the solution. All these equipment are appropriate for use and have proof to substantiate them. The *In vitro* dissolution test was performed using paddle dissolution equipment.

The steps involved in the dissolution test are:



Mechanical properties of the orodispersible films

The mechanical qualities of the ODF are also important for end-user handling. "Processes are taken during the fabrication of orodispersible films to ensure that they have sufficient mechanical strength to withstand handling without being destroyed," as per the European Pharmacopoeia [13]. However, tear resistance, tensile strength, and puncture strength are some of the most common tests conducted by researchers in this field.

Table 8: Mechanical characterization: property, technique, and equation

S. No.	Mechanical property	Technique	Equation	References
1	Elongation percentage (%E)	When a film sample is stressed, it stretches, which is known as a strain. Strain is defined as the distortion of a film divided by the sample's initial length.	%E = Increase in strip length X 100/ Original strip length	[71]
2	Tensile strength (TS)	An Instron TA. XT2 texture analyzer with a 5 kg load cell was utilized for this test. Using a force of 0.05 N, the ODF is clamped and dragged apart at a rate of 1 mm/s. It was calculated how much force was needed to break the ODF sample.	TS = Force at break/ Area of cross-section	
3	Folding endurance	This testing is conducted manually. The ODF with the same cross-sectional area is folded repeatedly till it fractures. The FE number specifies the number of folds the ODF sample can withstand before cracking. A large FE value indicates that ODF is linked to increased mechanical strength. The amount of plasticizer has an indirect influence on the FE.	The number of folding endurance is expressed as the number of folds.	
4	Tear resistance value (TRV)	It's the highest level of rupture resistance. The test is performed to evaluate how much force is needed to cause a tear. The loading rate in this investigation was 51 mm (2 in.)/min. The utmost force is discovered at the commencement of tearing.	TRV is expressed as a Newton	
5	Young's modulus (YM)	This is determined by dividing stress by strain	YM = Stress/Strain Stress = Force/Area (N/mm2) Strain = Change in length/ Original length (mm)	
6	Energy to puncture	A texture analyzer (TA. XT+, Stable Microsystems) and a Fifty N load are used in this test. The 5 mm circular probes were dropped at a velocity of 2 mm/s till they made contact with the ODF's surface. After that, the velocity is maintained at 1 mm/s until the film punctures. The calculations are performed using the appropriate equations.	Energy to puncture = AUC/V AUC = Area under the load displacement curve, V = Volume of film, Puncture Strength = F/Acs, F = Load required to puncture the film Acs = cross-sectional area of the film	
7	Elongation to puncture		Elongation to puncture = $\sqrt{R^2-D^2}$-R X 100/R R is the film's radius, D is the displacement of the probe	
8	Puncture strength		Puncture strength = Force/Area od cross section	

Surface pH

The pH of the developed films is likely to be impacted by the chemical composition of the drug and ingredients. After allowing the prepared films to moisten by leaving them in touch with distilled water for a brief length of time at ambient temperature, the surface pH of the films was measured. It was determined by touching the bulb of a pH meter [66, 67].

Content uniformity

The amount of API of each film is estimated to assess content uniformity. The consistency of the content is limited to 85–115%. The film was cut into desired sizes, dissolved in phosphate buffer pH 6.8, sonicated for a specific time, and filtered using Whatman filter paper. The final solution was subjected to UV analysis, after which the drug's concentration was calculated to ensure uniformity [68, 72].

Stability of orodispersible films

The quantity of water included in the ODF is extremely important because it mainly impacts one of the key quality attributes i.e. stability [44]. A lot of water in the film can make it adhesive or slippery, and it can also promote microbiological invasion [29]. Less water content, on the other hand, may result in a loss of film plasticizing effect [73, 74].

Furthermore, drug crystallization in ODF would have an essential effect on its biological characteristics. As a result, the drug in the ODF must remain amorphous at all times to prevent crystallization [75].

Packaging of orodispersible films

As ODFs are moisture sensitive, they require special packaging that protects them from moisture, and light and maintains their mechanical attributes. They depict various packaging choices for ODFs. Various packaging approaches have been suggested by Dixit and Puthli, including the use of lidding foils, aluminium foils, numerous-unit blisters, and dispensers with numerous unit dispensing options [30]. In a laboratory context, ODFs are usually packaged in aluminium pouches.

Patents of orodispersible films

Patents are techno-legal documents that are a type of intellectual property right. For example, A patent issued for one nation is only valid in that nation and not the other. As a result, the inventor must submit a patent application to every nation where the inventions will be commercialized and enforced. Many patent applicants travel throughout the world to file foreign patent claims under the Patent Cooperation Treaty, which is a well-known method Patent Co-operation Treaty (PCT). Anna Filipa and the team conducted a fast dissolving oral film evaluation that included a discussion of intellectual property concerns. Oral films (buccal, orodispersible, sublingual films) are all covered in this review. [41]. M. S. Gupta and colleagues have released an Indian patent viewpoint on ODFs, outlining the active members in India who are focusing on ODFs research and patent applications submitted in India. They conducted the review of current patent literature by using the United States Patent and Trademark Office (USPTO) and ESpacenet databases [76].

Fig. 12: Different types of packaging of orodispersible films

CONCLUSION

In conclusion, the QbD approach is a better approach for the formulation and evaluation of orodispersible films of antipsychotic drugs. As this approach involves the defining of QTPP, CQAs, risk assessment, design of formulation, preparation, and evaluation. It has distinct advantages like complete process understanding, elimination of batch failure, etc. ODFs are a comparatively new, adaptable, and patient-centered pharmaceutical dosage form in the field of personalized therapies, having distinctive attributes. Since they are compact and do not require water to be consumed, they have a lot of potential for increasing patient compliance in special populations. Due to its unique attributes, it is the best alternative dosage form for patients with mental disorders like schizophrenia, bipolar disorders, and psychosis. ODFs are placed at the surface of the tongue and quickly release the drug substance that is either ingested with saliva or absorbed through the mucosal membrane in the presence of penetration enhancers, resulting in greater bioavailability. For the manufacturing of ODFs, several fabrication processes are available, which include solvent casting, electrospinning, hot-melt extrusion, and printing technologies. One of the most difficult aspects of Orodispersible films is determining the API dose. Raising the thickness and/or surface area of the film, or creating numerous layers, is one technique to improve drug loading. However, a formulation such as this one may have a longer disintegration period and hence fail to secure patient compliance. ODFs, on the other hand, are perfect for giving potent medications in low doses, such as for the treatment of diseases associated with the nervous system such as schizophrenia, hallucinations, and mania.

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All authors have contributed equally.

CONFLICT OF INTERESTS

Declare none

REFERENCES

1. Quality by Design (QbD) in Pharmaceutical industry [internet]. Available from: https://www.pharmatutor.org/articles/quality-by-design-qbd-in-pharmaceutical-industry-tools-perspectives-and-challenges. [Last accessed on 21 Jul 2022]
2. Bhoop BS. Quality by Design (QbD) for holistic pharma excellence and regulatory compliance. Pharm Times. 2014;46(8):26-33.
3. Haque SE, Sheela A. Development of polymer-bound fast-dissolving metformin buccal film with disintegrants. Int J Nanomedicine. 2015;10Suppl 1:199-205. doi: 10.2147/IJN.S80052, PMID 26491321.
4. Bala R, Pawar P, Khanna S, Arora S. Orally dissolving strips: A new approach to oral drug delivery system. Int J Pharm Investig. 2013;3(2):67-76. doi: 10.4103/2230-973X.114897, PMID 24015378.
5. Adriany R, Anwar EF, Andrajati R. Hanafi M. Formulation of orodispersible tablet of Luffa acutangula (L.) roxb using novel co-processed via spray dried excipient. Int J Pharm Pharm Sci. 2015 Jan 1;7(1):124-9.
6. Das PS, Verma S, Saha P. Fast dissolving tablet using solid dispersion technique: a review. Int J Curr Pharm Sci. 2017;9(6):1. doi: 10.22159/ijcpr.2017v9i6.23435.
7. Tho I. Smeltetabletter fordeler og ulemper. Tidsskrift for Den Norske Legeforening. 2012;132(4):424-5.
8. Liew KB, Tan YTF, Peh KK. Characterization of oral disintegrating film containing donepezil for Alzheimer disease. AAPS PharmSciTech. 2012;13(1):134-42. doi: 10.1208/s12249-011-9729-4, PMID 22167416.
9. Singh S, Virmani T, Virmani R, Mahlawat G, Kumar P. Fast dissolving drug delivery systems: formulation, preparation techniques and evaluation. Univ J Pharm Res. 2018;3. doi: 10.22270/ujpr.v3i4.185.
10. Cilurzo F, Musazzi UM, Franze S, Selmin F, Minghetti P. Orodispersible dosage forms: biopharmaceutical improvements and regulatory requirements. Drug Discov Today. 2018;23(2):251-9. doi: 10.1016/j.drudis.2017.10.003, PMID 29030242.
11. NCI. Thesaurus [internet]. Available from: https://ncithesaurus.nci.nih.gov. [Last accessed on 21 Jul 2022]
12. In-process revision Vol. 35(5); Sep-Oct 2009. USP–NF [internet]. Available from: https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/pharmaceuticalDosageForms.pdf. [Last accessed on 17 Mar 2022]
13. Oromucosal Preparations. Physiol. In: European Pharmacopoeia Commission, editor. European pharmacopoeia. European directorate for the quality of medicines and Healthcare (EDQM). Strasbourg, France; 2018.
14. Gupta A, Kumar J, Verma S, Singh H. Application of quality by design approach for the optimization of orodispersible film formulation. Asian J Pharm Clin Res. 2018;11(14):8. doi: 10.22159/ajpcr.2018.v11s2.28508.

15. Meghana R. An overview on mouth dissolving film. Asian J Pharm Clin Res. 2018;11:44-7. doi: 10.22159/ajpcr.2018.v11s4.31712.
16. Frederic Deadman LL. New impregnated or coated films; 1967.
17. Fuchs P, Hilmann J. Medicament carriers in the form of film having active substance incorporated therein; 1979.
18. Pham CL, Wood AJ, Lambert MB, Carpenter W. Palatal erythema in patients using listerine cool mint pocketpaks oral care strips: case reports. J Dent Child (Chic). 2005 May-Aug;72(2):52-5. PMID 16294932.
19. Outsourcing-Pharma. Zengen claims a first with drug-laden oral strip [online]; 2022.
20. Preis M. Orally disintegrating films and mini-tablets-innovative dosage forms of choice for. pediatric use. AAPS PharmSciTech. 2015;16(2):234–41.
21. Reindel KL, DeAngelis MJ, Ferrara AS, Conn KM, Phillips EM, Corigliano AT. An exploratory study of Suboxone (buprenorphine/naloxone) film splitting: cutting methods, content uniformity, and stability. Int J Pharm Compd. 2019 May-Jun;23(3):258-63. PMID 31085795.
22. Tripathi KD. Essentials of medical pharmacology. New Delhi: Jaypee Brothers Medical Publishers (P), Ltd.; 2013.
23. Ozcan Bulbul EO, Mesut B, Cevher E, Oztaş E, Ozsoy Y. Product transfer from lab-scale to pilot-scale of quetiapine fumarate orodispersible films using quality by design approach. J Drug Deliv Sci Technol. 2019 Dec 1;54:101358. doi: 10.1016/j.jddst.2019.101358.
24. Jani R, Patel D. Hot melt extrusion: an industrially feasible approach for casting Orodispersible Film. Asian J Pharm Sci. 2015;10(4):292-305. doi: 10.1016/j.ajps.2015.03.002.
25. European Medicines Agency. ICH Q9 Quality risk management-European Medicines Agency; 2006.
26. Krull SM, Susarla R, Afolabi A, Li M, Ying Y, Iqbal Z. Polymer strip films as a robust, surfactant-free platform for delivery of BCS Class II drug nanoparticles. Int J Pharm. 2015;489(1-2):45-57. doi: 10.1016/j.ijpharm.2015.04.034, PMID 25888803.
27. Krull SM, Patel HV, Li M, Bilgili E, Dave RN. Critical material attributes (cmas) of strip films loaded with poorly water-soluble drug nanoparticles: I. Impact of plasticizer on film properties and dissolution. Eur J Pharm Sci. 2016;92:146-55. doi: 10.1016/j.ejps.2016.07.005, PMID 27402100.
28. Scarpa M, Paudel A, Kloprogge F, Hsiao WK, Bresciani M, Gaisford S. Key acceptability attributes of Orodispersible Films. Eur J Pharm Biopharm. 2018;125:131-40. doi: 10.1016/j.ejpb.2018.01.003, PMID 29355687.
29. Thabet Y, Breitkreutz J. Orodispersible films: product transfer from lab-scale to continuous manufacturing. Int J Pharm. 2018;535(1-2):285-92. doi: 10.1016/j.ijpharm.2017.11.021, PMID 29146537.
30. International BP. Practical considerations for DoE implementation in quality by design-BioProcess International [online]. Information Technology/practical-considerations-for-doe-implementation-in-quality-by-design-297328/>; 2022. Available from: https://bioprocessintl.com/manufacturing. [Last accessed on 21 Jul 2022]
31. Arya A, Chandra A, Sharma V, Pathak K. Fast dissolving oral films: an innovative drug delivery system and dosage form. Int J ChemTech Res. 2010 Jan;2(1):576-83.
32. Bhyan B, Jangra S, Kaur M, Singh H. Orally fast dissolving films: innovations in formulation and technology. Int J Pharm Sci Rev Res. 2011 Jul;9(2):9-15.
33. Dixit RP, Puthli SP. Oral strip technology: overview and future potential. J Control Release. 2009;139(2):94-107. doi: 10.1016/j.jconrel.2009.06.014, PMID 19559740.
34. Siddiqui MN, Garg G, Sharma PK. A short review of "A novel approach in oral fast dissolving drug delivery system and their patents". Adv Biol Res. 2011;5(6):291-303.
35. Dhere PM, Patwekar SL. Review on preparation and evaluation of oral disintegrating films. IJPT. 2011;3(4):1572-85.
36. Bhura N, Sanghvi K, Patel U, Parmar B, Patel D. A review on fast dissolving film. IJPRBS. 2012;1(3):66-89.
37. Dahiya M, Saha S, Shahiwala AF. A review on Mouth dissolving films. Curr Drug Deliv. 2009;6(5):469-76. doi: 10.2174/156720109789941713, PMID 19751197.
38. Gupta MM, Patel MG, Kedawat M. Enhancement of dissolution rate of rapidly dissolving oral film of meclizine hydrochloride by complexation of meclizine hydrochloride with β-cyclodextrine. J Appl Pharm Sci. 2011;1(9):150-3.
39. Smriti T. Mouth dissolving films: a review. Int J Pharm Biol Sci. 2013 Jan;4:899-908.
40. Murata Y, Isobe T, Kofuji K, Nishida N, Kamaguchi R. Preparation of fast dissolving films for oral dosage from natural polysaccharides. Materials (Basel). 2010 Aug 9;3(8):4291-9. doi: 10.3390/ma3084291, PMID 28883330.
41. Patel K, Soni S, Patel R, Pandya V, Bharadia P. Mouth dissolving film: a review. Int J Pharm Res Scholars. 2012;1(3):154-63.
42. Kumar SV, Gvaskar B, Sharan G, Rao YM. Overview on fast dissolving films. Int J Pharm Pharm Sci. 2010;2(3):2933.
43. Panchal MS, Patel H, Bagada A, Vadalia KR. Formulation and evaluation of mouth dissolving film of ropinirole hydrochloride by using pullulan polymers. IJPRAS. 2012;1(3):60-72.
44. Borges AF, Silva C, Coelho JF, Simoes S. Oral films: current status and future perspectives II– Intellectual property, technologies and market needs. J Control Release. 2015 May 28;206:108-21. doi: 10.1016/j.jconrel.2015.03.012, PMID 25776737.
45. Patent portfolio for pharmfilm® [internet]; 2018. Available from: https://aquestive.com/canadian-patent-portfolio-for-pharmfilm. [Last accessed on 21 Jul 2022]
46. Seoulpharmaceuticals; 2022. Available from: http://www.seoulpharmaceuticals.com/sub/sub1010.asp#expertize02> [Last accessed on 16 Mar 2022]
47. Borges AF, Silva C, Coelho JF, Simões S. Oral films: current status and future perspectives: I – Galenical development and quality attributes. J Control Release. 2015 May 28;206:1-19. doi: 10.1016/j.jconrel.2015.03.006, PMID 25747406.
48. Carolina Visser J, Weggemans OAF, Boosman RJ, Loos KU, Frijlink HW, Woerdenbag HJ. Increased drug load and polymer compatibility of bilayered orodispersible films. Eur J Pharm Sci. 2017 Sep 30;107:183-90. doi: 10.1016/j.ejps.2017.07.010, PMID 28709911.
49. Visser JC, Woerdenbag HJ, Crediet S, Gerrits E, Lesschen MA, Hinrichs WLJ. Orodispersible films in individualized pharmacotherapy: the development of a formulation for pharmacy preparations. Int J Pharm. 2015 Jan 15;478(1):155-63. doi: 10.1016/j.ijpharm.2014.11.013, PMID 25448577.
50. Łyszczarz E, Brniak W, Szafraniec Szczęsny J, Majka TM, Majda D, Zych M. The impact of the preparation method on the properties of orodispersible films with aripiprazole: electrospinning vs. Casting and 3D Printing Methods. Pharmaceutics. 2021 Jul 22;13(8):1122. doi: 10.3390/pharmaceutics13081122, PMID 34452083.
51. Illangakoon UE, Gill H, Shearman GC, Parhizkar M, Mahalingam S, Chatterton NP. Fast dissolving paracetamol/caffeine nanofibers prepared by electrospinning. Int J Pharm. 2014 Dec 30;477(1-2):369-79. doi: 10.1016/j.ijpharm.2014.10.036, PMID 25455779.
52. Rustemkyzy C, Belton P, Qi S. Preparation and characterization of ultra rapidly dissolving orodispersible films for treating and preventing iodine deficiency in the pediatric population. J Agric Food Chem. 2015 Nov 11;63(44):9831-8. doi: 10.1021/acs.jafc.5b03953, PMID 26499787.
53. Luraghi A, Peri F, Moroni L. Electrospinning for drug delivery applications: a review. J Control Release. 2021 Jun 10;334:463-84. doi: 10.1016/j.jconrel.2021.03.033, PMID 33781809.
54. Cilurzo F, Cupone IE, Minghetti P, Selmin F, Montanari L. Fast dissolving films made of maltodextrins. Eur J Pharm Biopharm. 2008 Nov;70(3):895-900. doi: 10.1016/j.ejpb.2008.06.032, PMID 18667164.
55. Maniruzzaman M, Boateng JS, Snowden MJ, Douroumis D. A review of hot-melt extrusion: process technology to pharmaceutical products. ISRN Pharm. 2012;2012:436763. doi: 10.5402/2012/436763, PMID 23326686.
56. Pimparade MB, Vo A, Maurya AS, Bae J, Morott JT, Feng X. Development and evaluation of an oral fast disintegrating anti-allergic film using hot-melt extrusion technology. Eur J Pharm Biopharm. 2017 Oct;119:81-90. doi: 10.1016/j.ejpb.2017.06.004, PMID 28596037.

57. Alomari M, Mohamed FH, Basit AW, Gaisford S. Personalised dosing: printing a dose of one's own medicine. Int J Pharm. 2015 Oct 30;494(2):568-77. doi: 10.1016/j.ijpharm.2014.12.006, PMID 25498157.
58. Jamroz W, Kurek M, Łyszczarz E, Szafraniec J, Knapik Kowalczuk J, Syrek K. 3D printed orodispersible films with aripiprazole. Int J Pharm. 2017 Nov 30;533(2):413-20. doi: 10.1016/j.ijpharm.2017.05.052, PMID 28552800.
59. Musazzi UM, Selmin F, Ortenzi MA, Mohammed GK, Franze S, Minghetti P, Cilurzo F. Personalized orodispersible films by hot melt ram extrusion 3D printing. Int J Pharm. 2018 Nov 15;551(1-2):52-9. doi: 10.1016/j.ijpharm.2018.09.013, PMID 30205128.
60. Sjöholm E, Sandler N. Additive manufacturing of personalized orodispersible warfarin films. Int J Pharm. 2019 Jun 10;564:117-23. doi: 10.1016/j.ijpharm.2019.04.018, PMID 30974195.
61. Khalid GM, Musazzi UM, Selmin F, Franze S, Minghetti P, Cilurzo F. Extemporaneous printing of diclofenac orodispersible films for pediatrics. Drug Dev Ind Pharm. 2021 Apr;47(4):636-44. doi: 10.1080/03639045.2021.1908335, PMID 33826438.
62. Myers GL, Hilbert SD, Boone BJ, Bogue AB, Sanghvi P, Hariharan M. Sublingual and buccal film compositions; 2013.
63. Niese S, Quodbach J. Formulation development of a continuously manufactured orodispersible film containing warfarin sodium for individualized dosing. Eur J Pharm Biopharm. 2019 Mar;136:93-101. doi: 10.1016/j.ejpb.2019.01.011, PMID 30660692.
64. Schmitz C, Bauer M, Linn M. U-shaped oral thin film; 2019.
65. Wood R, Mao HQ, KEET C, Martin R. Orally dissolving thin films containing allergens and methods of making and use; 2013.
66. Daud AS, Bonde MN, Sapkal NP. Development of zingiber officinale in oral dissolving films: effect of polymers on *in vitro*, *in vivo* parameters and clinical efficacy. Asian J Pharm. 2011;5(3):183. doi: 10.4103/0973-8398.91995.
67. Nair AB, Kumria R, Harsha S, Attimarad M, Al-Dhubiab BE, Alhaider IA. *In vitro* techniques to evaluate buccal films. J Control Release. 2013 Feb 28;166(1):10-21. doi: 10.1016/j.jconrel.2012.11.019, PMID 23219961.
68. Liew KB, Tan YT, Peh KK. Characterization of oral disintegrating film containing donepezil for Alzheimer disease. AAPS PharmSciTech. 2012 Mar;13(1):134-42. doi: 10.1208/s12249-011-9729-4, PMID 22167416.
69. Sievens Figueroa L, Bhakay A, Jerez Rozo JI, Pandya N, Romañach RJ, Michniak Kohn B, Iqbal Z, Bilgili E, Dave RN. Preparation and characterization of hydroxypropyl methyl cellulose films containing stable BCS Class II drug nanoparticles for pharmaceutical applications. Int J Pharm. 2012 Feb 28;423(2):496-508. doi: 10.1016/j.ijpharm.2011.12.001, PMID 22178619.
70. Lakshmi PK, Sridharan A, Sreekanth J. Formulation development of fast releasing oral thin films of levocetrizine dihydrochloride with eudragit®epo and optimization through taguchi orthogonal experimental design. Asian J Pharm. 2011;5(2):84. doi: 10.4103/0973-8398.84548.
71. Gupta MS, Kumar TP. Characterization of orodispersible films: an overview of methods and introduction to a new disintegration test apparatus using LDR– LED sensors. J Pharm Sci. 2020 Oct;109(10):2925-42. doi: 10.1016/j.xphs.2020.06.012, PMID 32565356.
72. Ahmed MG, Charyulu RN, Harish NM, Prabhu P. Formulation and *in vitro* evaluation of chitosan films containing tetracycline for the treatment of periodontitis. Asian J Pharm. 2009;3(2):113. doi: 10.4103/0973-8398.55048.
73. Hoffmann EM, Breitenbach A, Breitkreutz J. Advances in orodispersible films for drug delivery. Expert Opin Drug Deliv. 2011 Mar;8(3):299-316. doi: 10.1517/17425247.2011.553217, PMID 21284577.
74. Yir Erong B, Bayor MT, Ayensu I, Gbedema SY, Boateng JS. Oral thin films as a remedy for noncompliance in pediatric and geriatric patients. Ther Deliv. 2019 Jul;10(7):443-64. doi: 10.4155/tde-2019-0032, PMID 31264527.
75. Senta Loys Z, Bourgeois S, Briançon S, Fessi H. Characterization and stability study of tetrabenazine loaded in orodispersible films for pediatric therapy. International Journal of Pharmaceutics. 2018;536(2):503-4. doi: 10.1016/j.ijpharm.2017.08.029.
76. Gupta S, Kumar TP, Gowda DV. Patent perspective on orodispersible films. Recent Pat Drug Deliv Formul. 2020;14(2):88-97. doi: 10.2174/1872211314666200904104022, PMID 32885766.