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Review

Innovation in Orodispersible Dosage Forms and Its Role in Emergency Treatment

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Abstract

Most of the severe neurological conditions require prompt attention to avoid major damage due to various health related conditions such as seizures, hypoglycemia, cardiac arrest and unconsciousness. In such cases, if a trained medical practitioner is not available, it might lead to severe damage to the patient health condition such as neurological damage to a seizing patient. These issues have led to finding a solution for pharmaceutical manufacturers to design a convenient drug dosage form with quick action. Orodisperible dosage forms are gaining attention among manufacturer`s market due to cost-effective methods of preparation and for clinicians to address such critical situations to save Patient`s lives. The primary feature of orodispersible dosage form is the quick disintegration due to the use of the polymer known as superdisintegrants in the formulation. In this review, discuss various orodispersible drug delivery systems with their respective manufacturing methods are discussed. Also, the major features of this delivery system and mechanism of the superdisintegrants are discussed. Furthermore, dissolution and absorption pattern of the orodispersible dosage form is also explained. The highlights related to the use of the emerging technology of 3D printing in orodispersible films is also discussed. Finally, the conclusion for the application and importance of orodispersible tablets in emergency treatment i.e., epileptic seizures is provided.

Keywords

Orodisperible dosage forms, Superdisintegrants, Seizures, Emergency treatment, 3D printing technology, Orodipsersible films, Epilepsy

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1. Introduction

Since few decades, pharmaceutical scientists have strived to improve the developed dosage forms or drug delivery systems to achieve the best results in terms of efficacy, side effects, patient compliance, and cost-effectiveness [1-4]. The route of administration is an important factor considering the medical condition. However, solid or liquid oral drugs are still preferred over other dosage forms due to ease of administration, cost-effectiveness, and patient compliance [5]. Solid dosages are commonly manufactured forms among oral routes for stability and cost-effectiveness. Many advanced drug delivery systems have been developed pertaining to the release of drugs for optimum absorption in the gastrointestinal tract (GIT). However, in certain clinical conditions or emergencies, a patient might be unable to take solid oral dosage forms, thus, the self-administration of medicine is not possible, and necessary help is required [6].

Dysphagia is a widespread problem globally, covering about 35% of patients who cannot swallow solid drugs [7, 8]. Besides that, this problem is observed in various geriatrics and paediatrics cases. This condition may lead to unconsciousness, particularly in people with diabetes, and may lead to coma. Likewise, patients with psychological issues or seizures are serious situations where a patient needs to be intervened immediately. In such cases, if an expert medical practitioner is not available to administer the drug parenterally, it leads to an emergency resulting in death [9, 10]. To address these issues, an innovative solution must be considered to develop a dosage form for the oral route with a quick onset of action and cost-effectivity for manufacturing industries.

Some medical conditions require immediate treatment in a hospital setup where a patient may be unable to self-administer the medicines and need urgent therapy, such as hypoglycemia, cardiac arrest, epileptic seizures, and other psychological conditions in which the patient needs to be given relaxants to prevent any self-harm. A pharmaceutical scientist must aim to address both patient's and manufacturer's issues to develop a delivery system that could address all the above problems [11-13].

A relatively novel oral drug delivery system is gaining popularity for being the most sophisticated precise dosage form offering patient compliance and economy for both the patient and the manufacturer. The release of the drug in a few seconds due to rapid disintegration is the primary function of such dosage form known as the orodispersible drug delivery system [14].

In this review, the orodispersible tablets (ODTs) are explained as emergency medicine for patients with serious medical conditions requiring the drug to be immediately released after administration [15]. Moreover, mechanism of superdisintegrant and its role in the formulation is discussed in detail followed by the insights on the 3D printing technology in formulating ODTs are given with detail literature review.

2. Study Design

The study design was constructed by conducting a detailed literature review using different databases which includes pharmaceutical formulation development. A systemic literature review approach of highly cited and recent relevant research articles, book chapters and proceedings were studied. Some of the references are given below [16-18];

[16] Deore PD, Maru AM, More Y. Review on orodispersible tablet: Recent trends of manufacturing of orodispersible tablet. Research Journal of Pharmaceutical Dosage Forms and Technology. 2022, 14(2), 177-182. DOI: 10.52711/0975-4377.2022.00028
[17] Tran PH, Lee BJ, Tran TT. Strategies and formulations of freeze-dried tablets for controlled drug delivery. International Journal of Pharmaceutics. 2021, 597, 120373. DOI: 10.1016/j.ijpharm.2021.120373
[18] Chintamaneni PK, Thangavelu P, Chaitanya M, Ali HS, Usamo FB. Natural products as pharmaceutical additives in drug delivery systems. Plant polysaccharides as pharmaceutical excipients. Elsevier. 2023, 45-81. DOI: 10.1016/B978-0-323-90780-4.00024-33. Orodispersible Drug Delivery Systems

The orodispersible formulations are developed to disintegrate rapidly in the mouth, releasing the active ingredient readily and forming a solution/suspension with saliva without the aid of water [19]. The European Pharmacopeia [20] defines orodispersible formulations as drugs which disintegrate in < 3 minutes. However, practically orodispersible formulations generally disintegrate within 10 seconds to 1 minute [21].

Various orodispersible formulations are already available in the market and are widely accepted in place of conventional dosage forms. These orodispersible formulations are stable in their packaged form and rapidly disintegrate in the mouth, releasing the drug content immediately subjected to local absorption through the oral mucosa and further via pre-gastric absorption when the drug-loaded saliva passes through the GIT [22]. There can be a difference in the pharmacokinetic property of the drug due to different routes of absorption and rates within the GIT. Initially, orodispersible formulations were developed for dysphagia in elderly patients and children and accepted as the factor for patient adherence to the therapy [23, 24].

The surge in publications on orodispersible formulations in the last 24 years has given rise to a particular interest in medical sciences and pharmaceuticals as a business opportunity. The scientific data shows a growing interest in

orodispersible formulations for the geriatric and pediatric populations. Much research is ongoing using orodispersible formulations as a rescue medicine in emergencies. Among several types of orodispersible dosage forms, 66.3% of the reports pertain to orodispersible formulations [7, 25]. Several orodispersible formulations available in the market include [16, 26]:

(1) Oral lyophilates (ORLs)
(2) ODTs
(3) Orodispersible granules
(4) Orodispersible films
(5) While some forms are in the development stage which includes:
(6) Orodispersible minitablets (ODMTs)
(7) Fast disintegrating capsules
(8) Novel orodispersible formulations

In this study, ODTs are of particular interest to be presented as the stable and novel dosage form to be placed in the buccal cavity, where it disintegrates rapidly as soon as it gets in contact with the saliva.

3.1 Oral Lyophilates

ORLs are solid oral dosage forms where the drug molecules are prepared in the dispersion form, and then the solvent is removed through freeze-drying. The solution/suspension of the active drug is transferred into molds (blisters) and subjected to freeze-drying, forming solid tablets directly into the packaging blisters [27]. Typically, the excipients used are gelatin, alginates, or dextrans, which form the matrix of the tablets with mannitol as a bulking agent and glycine to prevent shrinkage on freeze-drying [7]. The freeze-drying technique is preferred for the tablet formulation of drugs with poor flow properties and low bulk density. Though ORLs have an obvious advantage for nanoparticle-based formulations, they are prepared with low pressure producing a porous structure that aids in rapid disintegration. But simultaneously, the high porosity leads to the weak mechanical strength of the tablets requiring special packaging. In addition, manufacturing ORLs requires a high amount of energy and long-duration methods with special packaging, thus increasing the products' overall cost, which adds a significant disadvantage to ORLs [17].

3.2 Orodispersible Tablets

According to European Pharmacopeia [20] specifications, ODT is an uncoated oral tablet that should completely disintegrate when placed in the mouth before swallowing in less than 3 minutes. However, US Food and Drug Administration (FDA) requires a disintegration time (DT) of 30 seconds for the ODTs [28], which is relevant to the actual administration condition and patient demand. The main characteristic of ODTs in this category is the DT. However, the evaluation test for DT does not simulate the *in-vivo* conditions, as traditionally, it is developed for conventional tablets. It is crucial to develop a new methodology to determine the DT using new apparatus and techniques to correlate the *in-vitro*-i*n-vivo* results for ODTs.

Several manufacturing methods have been proposed for ODTs, such as direct compression, cotton candy, phase transition, molding, mass extrusion, melt granulation, sublimation, etc. [7]. Freeze-drying is another preparation method for ODTs [29]. The direct compression method is widely accepted as the most convenient and cost-effective, requiring only a few steps of mixing and directly compressing the powder blend into tablets. Thus, the product has higher mechanical strength and special disintegrants may be added to decrease the DT [29].

The key ingredient in ODTs is the super disintegrant which is responsible for the rapid disintegration of the compressed tablet as soon as it gets in contact with the saliva through the process of swelling or wicking/capillary action of super disintegrant [30]. Among several other methods and quantity of the excipient-related factors, determining the swelling or wicking capacity of the different types of super disintegrants is vital in evaluating their efficiency for ODTs to bring the required DT. As the significant advantage of ODTs is for the problem of dysphagia in children, geriatrics, and certain disease conditions, the formulation brings a substantial drawback for the active drugs with an unpleasant and bitter taste [31, 32]. This may reduce patient compliance and preference for ODTs in normal conditions, especially when a patient is conscious enough to respond. For this purpose, several approaches have been made to add an appropriate flavoring agent and choose a better diluent, such as mannitol, for a good mouthfeel [7, 33, 34].

3.3 Orodispersible Minitablets

The ODMTs were first introduced in 2011 as small-sized tablets (less than 3 mm) for children. The formulation has both a small size and rapid disintegration in the mouth, avoiding the risk of particle aspiration and unpleasant mouthfeel. The unique features of ODMTs make them a feasible dosage form for pediatric and bedridden patients. The formulation is prepared by the direct compression method; however, the challenge is evaluating the DT using the typical disintegration apparatus used for conventional tablets. Such an apparatus is not suitable for assessing ODMTs. Hence improved and specialized test apparatus is proposed for ODMTs in the scientific literature, which is still not yet acceptable by regulatory authorities [7].

The ODMTs of size 2 mm/5 mg and 3 mm/20 mg containing lorazepam of 0.25 and 1.00 mg were prepared by Kotlowska et al [35] through the direct compression method using a precise powder pipette for accurate die filling. A disintegration test was performed using European Pharmacopeia [20] apparatus and simulated wetting time (SWT) tests, which both showed similar results.

3.4 Orodispersible Films

The Orodispersible Films (ODFs) are stamp-sized polymer films with or without active drugs to be placed on the tongue, where they instantly dissolve, liberating drug molecules for absorption. FDA uses the term 'soluble film' while the European Medicines Agency (EMA) uses the term formulation as ODFs. The concept of oral films was first found in patent data in the 1960s as a mouth freshener [36]. In 2003, the first ODF was formulated with active pharmaceutical ingredient (API), benzocaine as relief strips. ODFs are prepared mainly by solvent casting, where a viscous solution with API is cast onto a surface liner with the help of a film applicator. The film is then dried in an oven, followed by cutting into a suitable size oral dosage form (e.g., 2 × 3 cm) and packaged into moisture-protecting packaging. Another method, hot-melt extrusion, is a solvent-free method where API and excipient blend are heated to melt and form a dense preparation. It has the advantage of better drug loading and release but is unsuitable for heat-sensitive API. In addition, the film-forming polymers for the heat melt process are limited. Other methods include a rolling technique where a highly viscous solution is rolled onto a plane carrier surface followed by drying, spraying a drug-loaded solution, or suspension onto the already prepared film by solvent casting resulting in a multilayered film. Film-forming by electrostatic spraying is gaining popularity in pharmaceutical applications. A high electric field is applied to polymer solutions containing API, resulting in nanoscale polymer fibers having a high surface area and improved dissolution time [37].

There is a new approach to forming ODFs, i.e., the printing of API on a drug-free film obtained by solvent casting or a film already containing an API to form a combination of a drug product. This technology demands nano-sized particles of API, which are not commercially available yet

3.5 Other Orodispersible Dosage Forms

3.5.1 Fast Disintegrating Capsules

These modified hard gelatin capsules disintegrate in the mouth in less than a minute. Such capsules can be made using gelatin with low bloom strength (equal to 43) and hydrophilic excipients such as sorbitol, xylitol, and macrogols. The capsules have the advantage of high drug loading capacity that can be solid, and liquid prepared without special packaging. Perforation and vacuum drying were suggested as an alternate technique for preparing hard gelatin capsules [7].

3.5.2 Electrospun Fibers

Electrospun fibers are the nano and microscale fibers prepared by the electrospinning process. A thin jet of a polymer solution containing API is drawn into an electric field, producing nanofibers after evaporating the solvent. The nanofibers produced have a large surface area, accounting for immediate disintegration when mixed with water. The advantage of having a higher surface area and making amorphous material with improved solubility of APIs. The solvents usually used are organic, which is the main disadvantage of the formulation. However, water can be used as a solvent in the process for water-soluble polymers. The nanofibers, also known as nano-webs, are the recent advanced orodispersible formulations that lack data on the preference of this dosage form to be used by children or elderly patients [7].

4. Features of Orodispersible Tablets

4.1 Drug Disintegration and Immediate Release

According to FDA recommendations for orodispersible dosage forms, DT should be less than 30 seconds (FDA, 2008). An assumption has been made of the requirement for ODTs to disintegrate within a few seconds and completely dissolve in about a minute. Typically, DT is measured with standard disintegration test methods used for conventional tablets. However, the *in-vitro* setting ideally does not reflect the environment ODT experiences in the mouth. Hence, the modified test methods must be developed for ODTs [38-40].

4.1.1 Super Disintegrants

An ideal ODT must have rapid buccal disintegration without water for swallowing. Several methods have been investigated to achieve fast DT, such as low compression force to form a porous formulation for rapid disintegration, the use of fast-dissolving water-soluble excipients, and super disintegrants [30]. The addition of effervescent materials has also been observed to enhance disintegration. However, since the material is moisture-sensitive, specialized packaging is required to control humidity and temperature [41].

Disintegrants are the materials that break the tablet matrix to release the active drug efficiently for dissolution. Chemically, disintegrants are classified as clays, starches, cellulose, gums, algins, and cross-linked polymers. A group of materials known as 'super disintegrants' has gained popularity as rapid disintegrants. They are named after their efficiency at very low concentrations (2-4%). The most commonly used super disintegrants, crospovidone, croscarmellose, and sodium starch glycolate, are examples of cross-linked polymer, cellulose, and starch, respectively. In addition, a large variety of materials have also been reported to possess good disintegrating properties, which include methylcellulose, bentonite, veegum HV, natural sponges, cellulose, wood products, guar gum, alginic acid, carboxymethylcellulose, cation-exchange resins, citrus pulp, and agar [18, 42].

4.1.1.1 Mechanism of Action of Super Disintegrants

The use of super disintegrants has paved the way for the development and understanding of the theories of their working mechanism, which has made it easier for researchers to select the most suitable super disintegrant for the formulation. The most widely accepted mechanism by which super disintegrants function is water uptake through wicking/capillary action, swelling, or plastic deformation [30].

(1) Swelling

Almost all super disintegrants have a swelling property depending upon the pH level of the medium. As the material within the tablet absorbs solution in an aqueous medium, it starts to swell and expand, creating internal pressure and breaking the matrix of the tablet, bringing about rapid disintegration of the tablet [3, 30].

(2) Wicking

Wicking is a capillary action where the aqueous medium seeps into the tablet through a porous structure, weakening the bonds between excipients and causing the tablet to break, facilitating disintegration. A super disintegrant may function by capillary and swelling action [3].

(3) Plastic Deformation

Super disintegrants with plastic deformation properties have a good role in disintegration. Upon compression, the particle is deformed. As soon as it comes in contact with the aqueous medium, it returns to its original shape with swelling action causing intrinsic pressure within the dosage form, breaking the tablet matrix. Additionally, effervescent material can also aid disintegration by liberating carbon dioxide gas on exposure to an aqueous medium or stomach acid causing tablet internal pressure to facilitate fast breakdown. It is a typical acid/base reaction in a tablet containing bicarbonates [43].

(4) Characterization of Super Disintegrants

Since the release of the active drug from the tablet depends upon the performance of the super disintegrants, the evaluation and characterization of the super disintegrants is essential to understand the overall role of the ODTs. However, the methods for the quantitative evaluation of tablet disintegration are limited, even less for wicking action. The tablet disintegration is characterized visually through photography or videography. The United States Pharmacopeial (USP) disintegration apparatus is still used for ODTs as the only resort since an ideal method has not yet been approved for ODTs [44].

Another method for the characterization of super disintegrants is through gravimetric or volumetric measurement. The swelling capacity of the super disintegrants in free form and within the tablet may show different results due to the impact of compression for the latter. Some of the methods used for in vitro evaluation of the function of super disintegrants reported by Joshi [45] are as follows;

(5) Gravimetric Swelling

This test was performed to evaluate the swelling behavior of the super disintegrant itself. The powder (2 g) was passed through sieve no. 120 into a beaker containing 100 ml water under constant stirring. At specific time intervals (1, 5, 10, 15, 20, and 30 min.), the content was filtered and blotted gently with tissue paper to remove water from the surface, and the swollen mass was weighed. The method was repeated at each interval, and the swelling index was calculated at each time by the following formula (1):

$$\text{Swelling Index} = (W_s - W_d)/W_d \quad (1)$$

W_s = Swollen mass (g)

W_d = Dry powder (g)

(6) Swelling Pressure Measurement

The swelling pressure of super disintegrants in a tablet is measured using a texture analyzer. The device is composed of a chamber that holds the tablets inside it. To one end, attached is the semi-permeable membrane where the tablet is to be placed, and on the other, a plunger can move inside the chamber without touching the walls to avoid friction. The chamber is placed in a dry beaker with the tablet centered inside the beaker over the semi-permeable membrane. As the aqueous medium is poured into the chamber, it passes through the semi-permeable membrane reaching the ODT (Figure

1). As the tablet starts swelling, pressure is exerted on the plunger, and it moves upside, placed just above the surface of dry ODT. The instrument begins to record the pressure through probes, and the swelling pressure (g) is plotted against time [45].

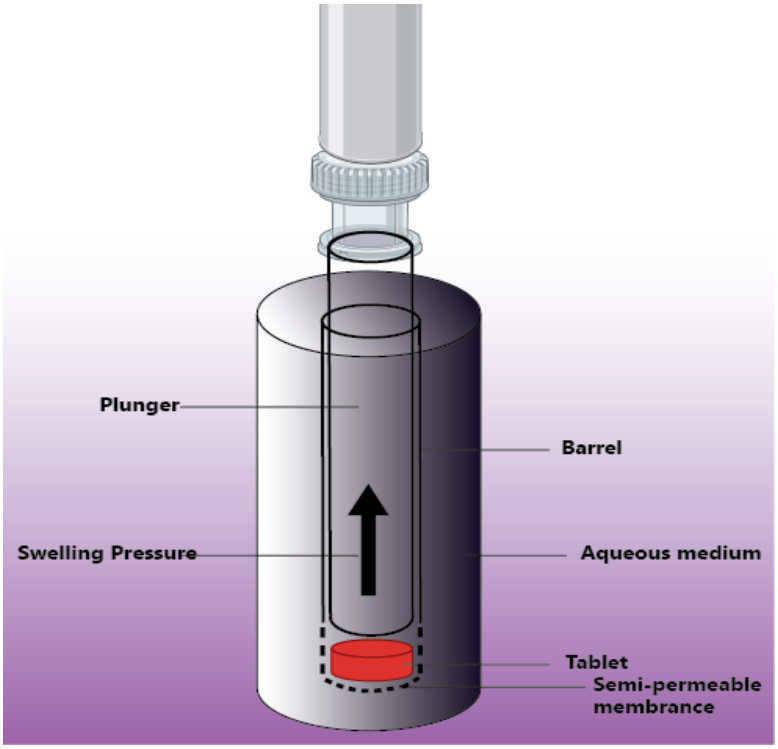

Figure 1. Schematic diagram of a modified texture analyzer.

(6) Water Desorption Study or Wetting Time

The wet mass obtained from gravimetric measurements is further analyzed to understand the nature of the super disintegrant's water-absorbing capacity. The wet mass is placed on the filter paper, absorbing water from the swollen mass. This process is observed for 2 minutes. The radius of the waterfront on the filter paper over the radius of the wet mass is taken to characterize the swelling further and free/bound water. Some disintegrants are found to retain the water. In contrast, others lost the absorbed water [45].

(7) Water Uptake Study Using Fourier-Transform Infrared Spectroscopy

Barmpalexis et al [46] proposed a method to evaluate the moisture content inside the super disintegrants after hydration with accuracy using Fourier-Transform Infrared Spectroscopy (FTIR) spectroscopy at a sub-molecular level as described by the method proposed by The polymers were hydrated with water and the abosrbances were taken at different time intervals. OH-banding shows profound continuous uptake of water molecules into the matrix of polymer differentiating the capacity of uptake of water by different polymers. The results were further assisted by theoretical modeling using molecular dynamic simulations where diffusion coefficient of water was calculated assuming the data fitting into fickian one dimensional diffusion [47].

5. Drug Dissolution and Absorption

Followed by rapid disintegration in the mouth, the next important parameter for a formulation to address is the dissolution of the drug for absorption. Some pharmacokinetic studies reported that ODTs have better drug bioavailability than conventional tablets with an increased absorption rate [48, 49]. However, the drug still cannot avoid first-pass metabolism [32, 50], but at the same time, some researchers have reported that it will prevent it [51]. The drug dissolved in the saliva passes into the GIT, and the absorption rate varies throughout the tract. The drug also encounters different pHs beginning from mouth to stomach and small intestine, as in the conventional dosage form. Hence, pH parameters are essential when formulating ODTs with poorly soluble and pH-sensitive drugs [52]. It has been concluded that ODTs perform better than conventional tablets. Still, they cannot be compared with the bioavailability of drugs achieved by the IM/IV route of administration. Simulated *in-vitro* testing should be compared with the *in-vivo* condition as closely as possible to study the dissolution of the drug from ODTs [53]. For dissolution studies in each compartment described in Table 1, three parameters should be considered such as [53, 54]:

(1) The pH of the medium;

(2) The volume of the medium;

(3) Residence time for a drug.

5.1 Mouth

In the case of ODTs, some drugs are also absorbed into the systemic circulation through the oral mucosa. As the drug starts to disintegrate, the average residence time for a dosage form in the mouth is 3 minutes before the saliva drug solution is swallowed completely. Saliva is composed of water, mucus, protein amylase, and minerals. The salivary glands also produce saliva upon stimuli, so the saliva volume is typically 3-5 ml. The pH of saliva is usually within the range of 6.2-7.4. In the biorelevant *in-vitro* testing, the ODTs must be allowed to disintegrate in 5 ml/unit of simulated saliva (Table 1). Sampling must be performed with very short intervals, ideally from 30 seconds to 3 minutes [55].

5.2 Stomach

As ODTs do not require the aid of water to swallow the tablet, the stomach is considered to be in a fasting state, with the stomach medium volume as low as 50 ml (Table 1). If the dosage form is taken with water, the volume of the stomach goes upto 200-250 ml with a pH range of 1.5-1.9 [56], while the gastric emptying time in a fasted stomach, on average, is taken as 1 hour [57]. Hence, *in-vitro* dissolution testing must be performed with the medium to simulate the fasted stomach. As the solution/suspension of the drug enters the stomach, 5-8 ml of the same is added in the 50-250 ml of stomach simulated medium. Sampling should be done frequently during the first 5-30 minutes to evaluate the dissolution of the drug in stomach media [53].

Table 1. Biorelevant dissolution model in fasting conditions.

Dissolution Media (Fasting Condition)				
GI Tract	**Type**	**pH**	**Volume (ml)**	**Residence Time (min.)**
Mouth	Simulated saliva	6.2-7.4	5.0	0.3-3.0
Stomach	Simulated gastric fluid	1.5-1.9	50.0	5.0-30.0
Small Intestine	Simulated intestinal fluid	6.5	250.0	60.0-240.0

5.3 Intestine

The average volume of intraluminal fluid is 250 ml in a fasted condition, having a pH level of 6.5 (Table 1). The residence time of the drug within the small intestine is about 1-3 hours [57]. When the fluid-containing drug enters the intestinal media, the *in-vitro* dissolution evaluation should mimic the intestinal dissolution medium containing simulated stomach fluids. The experiment is performed at a temperature of 35 ± 0.5°C. All the dissolution test experiments modified for ODTs must comply with USP and BP [53].

6. Recent Advancement: 3D Printing Technology in Orodispersible Films

According to the International Standard Organization (ISO), 3D printing is defined as: “Fabricating objects by depositing the materials using printer technology” [58]. This technology is confined to solid dosage forms for customized medication Moreover, 3D printing technology has an advantage of designing multiple drug formulation for multi-drug therapy in a single dosage owing to patient compliance [59]. Personalized treatment achieves the best therapeutics results and hence the dose is adjusted according to the patient`s disease condition. Table 2. comprehensively describes the various orodispersible dosage forms prepared through different method of preparations along with the type of superdisintegrants. Özcan-Bülbül et al [58] prepared Montelukast-loaded ODFs through 3D printing technology for oral delivery. Various 3D printing techniques have been explored for the manufacturing of 3D printed dosage forms such as the fused deposition method (FDM), Hot-melt extrusion (HME) and print-fill using thermoplastic polymers as primary components of the formulation. Among them, the FDM is the most suited one for developing customizable controlled release formulations, however, feasibility of HME 3D printed formulations was also explored [60]. Several customizable orodispersible formulations using 3D printing technology were developed and investigated. Rodríguez-Pombo et al [61] developed orodispersible films using inkjet printing technology with fixed doses of hydrocortisone-loaded inks. In another study, curcumin and phycocyanin, two different functional materials, were printed simultaneously on orodispersible films using a coaxial nozzle where the active were encapsulated in liposomal material, curcumin in the outer core and phycocyanin in the inner core of the liposome [62]. Racaniello et al [63] also developed a novel oral mucoadhesive orodispersible films containing Clobestasol propionate in paediatric treatment of Oral Lichen Planus. The film was prepared by Direct Powder Extrusion (DPE) 3D printing technique. The first FDA approved ODF manufactured through 3D printing technology using the Zip®Dose technology was SPRITAM® (levetiracetam) (Langhorne, PA, USA) [64]. Hence, several studies have proved the success of the customizable orodispersible dosage forms using 3D printing technology which opens the doors for healthcare professionals to achieve optimum treatment strategy for patients.

7. ODTs in Emergency Condition: Epileptic Seizures

Acute repetitive seizures (ARS) are a series of frequent seizures for which immediate treatment is required. When a patient is identified with ARS, concerns are associated with seizures risk arise, which include injury during an uncontrollable seizure, negative impact socially and economically from frequent emergency visits, psychosis, and the most critical risk of status epilepticus, which may lead to neurological damage or death [65]. Convulsive status epilepticus is the most common neurological emergency with a high morbidity and mortality rate. Status epilepticus is a seizure or a series of seizures that lasts 30 minutes or more without gaining complete consciousness. A seizure that prolongs after 5 minutes cannot be stopped until the medication is given. For a medical emergency like status epilepticus, early treatment with an effective rescue medicine before admission to a hospital emergency with easy administration is required [66]. The International Guidelines for Seizure Management in Children and Adults recommends benzodiazepines as the first-line emergency treatment for seizures that lasts longer than 5 minutes. Lorazepam is given as the first choice of drug, while diazepam or midazolam are also commonly given when IV/IM administration is available, which is usually possible only in a hospital setup. However, alternatives are preferred in a pre-hospital or emergency condition through rectal or intranasal routes when IV drug administration is not possible [67]. For the past two decades, rectal formulations and IV administration of benzodiazepines have been the sole US FDA-approved medications for the out-of-hospital treatment of acute seizures. In 2020, FDA approved a new intranasal formulation as a rescue medication for epileptic seizures. In addition, an oral/buccal solution has already been approved in USA and Germany for pre-operative sedation in children [68]. Rectal diazepam has social limitations, while intranasal midazolam requires a particular device with training and patient cooperation to administer the drug properly. The buccal midazolam has been found easy to administer and recommended in the National Institute for Health and Care Excellence guidelines as the first choice, which has an efficacy to terminate seizure activity within 5-10 minutes of administration by 27-84% [67].

OD system is an advanced development in drug delivery and has gained popularity in the pharmaceutical industry due to its unique properties and advantages over conventional dosage forms. Pharmaceutical technologists have tried their best to develop orodispersible drug delivery systems. In the last decade, orodispersible technology has gained the attention of many scientists and industries and has become the fastest-growing venture for oral drug delivery systems. ODTs are widely accepted as an innovative variant of conventional tablets with simple and convenient manufacturing methods and ease of administration, addressing the need of both manufacturers and patients. Initially, the purpose of developing the ODTs was to overcome the problem of dysphagia in children, elderly patients, or patients with neuropsychological issues who could not self-administer medicines. Keeping in mind the primary purpose of the formulation, ODTs can have a broad scope to be used in emergencies where the patient needs immediate treatment. orodispersible drug delivery systems can play a significant role as rescue medicines in emergencies such as epileptic seizures [69].

Table 2. Various methods of preparation of orodispersible dosage forms.

S. No:	Method	Drug	Disintegrants	Refs
1.	Wet Granulation Method	Oxcarbazepine	Ac-Di-sol	[70]
2.	Direct Compression Method	Carbamazepine	Crospovidone	[71]
3.	Direct Compression Method	Carbamazepine	Crospovidone, Crosscarmellose Sodium, Sodium starch glycolate	[72]
4.	Solid Dispersion Method	Carbamazepine	Croscarmellose sodium	[72]
5.	Solid Dispersions by Kneading Method	Carbamazepine	Sodium starch glycolate, cyclodextrin	[73]
6.	Direct Compression Method	lamotrigin	Kyron T-314 and sodium starch Glycolate	[74]
7.	Direct Compression Method	Clobazam	Crospovidone	[75]
8.	Direct ink Writing	Paracetamol, Caffeine, and Theophylline	Carboxymethyl Cellulose	[76]
9.	Solvent Casting Technique, 3D Printing Technique with a Hot-Melt Extrusion (HME)	Aripiprazole	Hydroxypropyl Cellulose	[77]
10.	Direct Powder Extrusion (DPE) 3D Printing Technique	Clobetasol Propionate	Hydroxypropylmethylcellulose or Polyethylene oxide blended with chitosan	[63]

8. Conclusion and Future Perspectives

Orodispersible drug dosage forms have potential advantage for emergency situations such as epileptic seizures and improved patient compliance have already raised market demand and manufacturer`s attention due to cost-effective methods of preparation. With improved biopharmaceutical properties and quick release of drug, orodispersible formulations are gaining more attention among various factions of society. Several types of orodispersible formulations are investigated using different methods such as orodisperisble tablets, orodispersible films, oral lyophilates etc. This innovative formulation has opened up ways to advancements such as 3D printing technology for individualized drug dosing for customizable treatment. This personalized drug approach has increased the demand for application of this technology in pharmaceutical industry although it is still in its early phase. Future of orodispersible formulations is the 3D printing technology which is catching attention of many researchers for the technique`s customizable drug dose delivery, however, certain limitations to 3D printing technology such as cost, material, and post-manufacturing problems need to be addressed. Other than that, nanoparticle based-orodispersible formulations can be further explored for enhanced drug delivery and absorption in several emergency conditions such as Migraine attack, Cardiac Attack and several neurological conditions.

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Conflict of Interest

The authors declare that they have no competing interests that can influence the work reported in this work.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Abbreviations

API: active pharmaceutical ingredient
ARS: Acute repetitive seizures
DT: disintegration time
FDM: fused deposition method
FTIR: Fourier-Transform Infrared Spectroscopy
GIT: gastrointestinal tract
HME: Hot-melt extrusion
ODMTs: Orodispersible minitablets
ODTs: orodispersible tablets
ORLs: Oral lyophilates
SWT: simulated wetting time

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