



## Advanced Methods for Fast Dissolving Films Preparation

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### Abstract

Fast-dissolving drug delivery systems have been created in place of traditional dosage forms for administering drugs for chronic conditions. Fast-dissolving films are more popular than conventional tablets and capsules in masking the bitter taste of medicines to enhance patient adherence. Quickly dissolving films are composed of an ultra-thin strip that dissolves under one minute when placed on the tongue. Dissolvable oral thin films, like breath strips, have been available for the last few years and have been well-received by consumers for administering vitamins, vaccines, and other medications. The review also thoroughly explains the different methods used in film production. The current review outlines the most recent patents related to fast-dissolving films. A short analysis was conducted on numerous factors used to assess these movies. Regarding long-term illnesses, fast-dissolving films are more effective for administering drugs and achieving quicker therapeutic blood levels than traditional oral forms.

**Keywords:** Fast-dissolving film; Preparation; pharmacokinetics; solvent casting method; design of experiment approach.

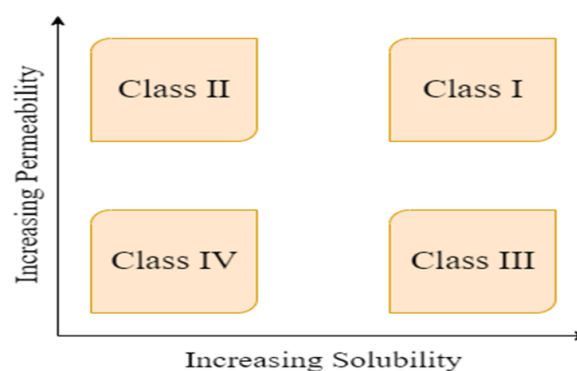
### 1. Introduction

Most patients prefer oral drug delivery as the most convenient route of administration (Lou et al., 2023). It provides painless, non-invasive, and portable benefits, improving therapeutic outcomes and patient compliance, particularly for chronic conditions (Shahiwala, 2011). For the drug to be developed in oral form, it must possess attributes like stability in the stomach's acidic environment, suitable hydrophilic-lipophilic balance for crossing the gastrointestinal membrane, and minimal gastrointestinal toxicity and irritation. While most

patients generally like it, certain drugs have some drawbacks because of their physicochemical characteristics, like poor permeability, limited solubility in gastric fluids, instability, and rapid metabolism. The factors mentioned above result in reducing the availability of drugs and presenting a challenge in adjusting the active pharmaceutical ingredients to meet acceptable levels of drug concentrations after oral administration or in finding a method to safeguard the targeted drug from degradation before entering the bloodstream (Salawi, 2022; Srebro et al., 2022).

Poor bioavailability can be anticipated for the drugs (excluding the drugs that non-substrates to active transporter or efflux mechanism) by Lipinski rule of 5 which is introduced by Lipinski who specifies the following four properties for poor bioavailability (1) high lipophilicity ( $\text{Log } P > 5$ ), (2) high molecular weight (more than 500 D), (3) molecules with more than 5 H-bond donors (e.g., OH and NH<sub>2</sub>), and (4) the presence of more than 10 H-bond acceptors (e.g., N and O) (Benet et al., 2016). In conclusion, the following points can be correlated to either insufficient aqueous solubility (1 and 2) or poor intestinal permeability (1, 3, and 4) (Pollastri, 2010). The objective while administering the medication to the human body is to ensure optimal solubility and, as a result, bioavailability while safeguarding the compound from harsh acidic environments and the 1<sup>st</sup> pass metabolism process. (Milligan & Saha, 2022). Most new chemical entities (NCEs) have low solubility in aqueous environments at physiological pH, which means that the rate at which they dissolve in gastrointestinal fluids determines how quickly they can enter the bloodstream. As per USP 2023, the solubility of the compound can be categorized based on the parts of diluent needed to dissolve the solute: very soluble (Less than 1), freely soluble (1 to 10), soluble (10 to 30), sparingly soluble (30 to 100), slightly soluble (100 to 1,000), very slightly soluble (1,000 to 10,000), practically insoluble, or insoluble (Greater than or equal to 10,000) (Fink et al., 2020). The drug molecules can be classified concerning their solubility and permeability according to The Biopharmaceutical Classification System (BCS), which is a framework for categorizing drug molecules based on solubility and permeability, into the following classes: class I high solubility and high permeability, class II low solubility and high permeability, class III high solubility and low permeability and Class IV with limited solubility and permeability. Based on that, the limited solubility is correlated to Class II and IV. (Pathak & Raghuvanshi, 2015) as shown in **Figure 1**. The limited bioavailability of such drugs will lead to higher dose intake to achieve the minimum effective concentration (MEC) and maintain the concentration more than MEC, thus increasing the probability of raising the adverse events of the drugs, especially for synthetic molecules, and leading to economic loss. The fundamental problem over the years has been to develop techniques that will allow most medications, regardless of their properties, to be administered orally to attain systemic therapeutic

availability. Many approaches have been explored to increase the water solubility of poorly water-soluble drugs (PWSDs) and, thus, their bioavailability (Sareen et al., 2012; Savjani et al., 2012). These techniques can be summarized as follows: (a) Physical modifications such as particle size reduction, crystal habit optimization, cocrystal formation, and solid dispersions. (b) Chemical modifications include buffer utilization, salt formation, and complexation (Cyclodextrins). (c) Miscellaneous methods include surfactants, co-solvents, hydrotrophy, supercritical fluids, and lipid-based drug delivery systems.



**Figure 1: The biopharmaceutical classification system (BCS)**

## 2. Fast Dissolving Films

Fast-melting films are a recent method of taking medication by mouth that provides quick effects while safeguarding against stomach acidity and the first-pass effect since the disintegration and absorption processes happen in the mouth. It is a dry form of medication that acts quickly. Fast-dissolving films are preferred over other drug delivery systems for children and older patients because they are easy to use. Lately, several studies have been released by researchers on various new polymer-based fast-dissolving films, such as fluoxetine (Rédai et al., 2021), metoclopramide hydrochloride (Reveny et al., 2017), lamotrigine (Hamza, 2017), ondansetron hydrochloride (Koland et al., 2010), olanzapine (Maher et al., 2016), and tenoxicam (Abdulelah & Abdulbaqi, 2021). Different methods can be used to create fast-dissolving films, like solvent casting, which involves blending the polymer solution with the plasticizer and drug solution, mixing, removing air, transferring to a dish, and heating to remove the solvent (Abdulelah & Abdulbaqi, 2021). Additional techniques include hot melt extrusion (Javeer & Amin, 2014), semisolid casting, solid dispersion

extrusion, and rolling (Hoffmann et al., 2011). A recent method was employed to create quick-dissolving forms by using a spinning agent that quickly dissolves the desired drug and is combined with the polymer solution (Sevinç Özakar & Özakar, 2021).

### 3. Main Components of Fast Dissolving Films

#### 3.1. Polymers

The rational selection and focusing of polymers are critical factors in creating a successful Fast dissolving film, as the mechanical strength of films is closely linked to these elements. Film properties can be modified by using them alone or with other polymers.

The level of recycled polymers is also crucial in creating a Fast-dissolving film (Lin et al., 1995). Selecting polymer type and concentration is essential for maintaining the integrity of fast-dissolving oral films. Typically, the polymer content in the production of films is approximately 45% of the dry strip's total weight, but it can be raised to 60–65% to achieve the desired film properties. Error! Reference source not found.. - A chart displaying data. Demonstrates the necessary characteristics for a Polymer to function as a film-forming agent in creating thin strips.

**Table 1 Properties for Ideal polymer:**(Liew et al., 2014)

Properties
Non-irritant
Should not hinder the disintegration time of ODF
Affordable
Should possess adequate shelf-life
Should possess good spreadability
Should exhibit sufficient tensile strength
Should have good mechanical properties
Non-toxic
Non-irritant

Various polymers are used to control the characteristics of the films, as listed in Error! Reference source not found.. Pullulan improves

flexibility. Films containing pullulan exhibit high tensile strength and stability across various temperatures. Different weights of gelatin molecules impact the characteristics of films made, with better films achieved by using polymers with higher molecular weights. The mixture of chitosan with high methoxy pectin (HMP) or low methoxy pectin (LMP) produces a top-notch strip. Cellulose-based polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose (MC), and carboxymethyl cellulose (CMC) produce films that have lower water vapor barrier properties because of their hydrophilic characteristics. Polyethylene glycol (PEG) has good film-forming properties whether used by itself or when mixed with other polymers (Centkowska et al., 2020; Liew et al., 2014; Pichayakorn et al., 2013; Singh et al., 2018). HPMC is an effective film-forming agent with various grades like Methocel E3, Methocel E5, Methocel E15 Premium LV, etc. Using multiple types of HPMC in the preparation process, it was revealed that Methocel E15 Premium LV produced fast dissolving films with desired characteristics. The desired physical and chemical properties were observed in the fast-dissolving film of famotidine made with HPMC and polyethylene glycol (PEG) (Irfan et al., 2016). Piroxicam, a drug not soluble in water, was added to fast-dissolving films made with maltodextrins (MDX) and the same low amount of dextrose (Cilurzo et al., 2008). Different HPMC, pullulan, and PVP concentrations significantly impact the mechanical properties and drug release of nebivolol HCl ODFs (Parejiya et al., 2013). Polymers control the release profile, so mono- and double-layered Bucco adhesive films of chlorhexidine were created to demonstrate this concept (Juliano et al., 2008). Films made with alginate, HPMC, and chitosan provide improved control over drug release. The impact of polymer concentration on the mechanical properties and strength of pullulan and HPMC-based ODFs of granisetron hydrochloride was demonstrated through manufacturing. Films made with 40–45% concentration of Pullulan did not have satisfactory properties, while films containing up to 40% HPMC were challenging to remove. Moreover, the adhesiveness of the film rose when the HPMC concentration exceeded 50% (Bodini et al., 2019). Research on creating Fast-dissolving films of losartan potassium with varying levels of maltodextrin (MD) and polyvinyl alcohol (PVA) showed that the time taken for the film to disintegrate in an artificial environment increased

solubility while also boosting

**Table 2: Most used natural and synthetic polymers.**

Type of polymer	Examples
Natural	Starch, polymerized rosin, pullulan, sodium alginate, Pectin, gelatin, and maltodextrins
Synthetic	Polyvinyl alcohol, hydroxy propyl methyl cellulose, sodium carboxy methyl cellulose, polyvinyl pyrrolidone, and hydroxy propyl cellulose

with higher polymer concentrations (Karolewicz, 2016). An additional study showed that pullulan is the most effective film-forming agent out of all the polymers examined (Kulkarni et al., 2010). Thin and brittle fast-dissolving films of cetirizine were created with 2% w/v pullulan, prompting increased concentration. By testing on Sprague-Dawley rats, the pharmacokinetic properties of the sample film of levocetirizine containing pullulan can be compared to the reference (oral solution of pure drug) to evaluate the performance of ODFs (Mishra & Amin, 2011).

### 3.2. Plasticizer

Incorporating a plasticizer into the formulations enhances mechanical properties like tensile strength and percent elongation (Liew et al., 2014). The plasticizer typically falls between 0% and 20% by weight. Examples of plasticizers commonly used include PEG, glycerol, diethyl phthalate, triethyl citrate, and tributyl citrate (Vishvakarma, 2018; Vuddanda et al., 2017). Plasticizers are commonly utilized in orally disintegrating film (ODF) formulations, as specified in Error! Reference source not found..

## 4. Methods of Preparation of Fast-Dissolving Films

### 4.1. Solvent Casting Method

The oldest technique for preparing FDFs is solvent casting. This method is water-based and capable of handling stable or unstable drugs to heat, allowing for the preparation of dosage forms without requiring solvent and thus evaporating through heating (Pechová et al., 2018; Reveny et al., 2017). To prepare active pharmaceutical ingredients or plant extracts, active substances are first dissolved in distilled water or a volatile solvent that allows the drugs to dissolve quickly and then mixed

thoroughly with a magnetic stirrer for consistency. The choice of solvents is based on the characteristics of the active substances. These characteristics include the active ingredient's compatibility with excipients, particularly film-forming polymers; compatibility between solvent and drug; temperature sensitivity; and polymorphic qualities. The film-forming polymer, coloring agent, plasticizer, and necessary excipients are individually prepared in distilled water. Once the required solution is ready, it is stirred again for consistency, commonly known as the film dope.

The film dope is then distributed on Petri dishes in a lab setting, and the Petri dishes are inserted into a hot oven at 40–50 °C for 24 hours. Once thoroughly dried, the films are cut into the required sizes and stored in aluminum foil for analysis. Broadly, film dope is applied to impregnated paper using solvent-cast film deposition methods. The dispersed media is transferred from a convection chamber to remove the solvents. After drying, the films are sliced into small sections and individually wrapped in aluminum foil or stored in sealed pouches. Taking preventative measures to protect against moisture is necessary when packaging films. Moisture negatively impacts the stability and mechanical characteristics of films. Furthermore, the temperature must be controlled to preserve the viscosity of solutions (Basu et al., 2022).

The solvent casting method is the most suitable method for preparing heat- and light-sensitive active ingredients, as it requires lower temperatures for the volatile ingredients and solvent removal from the films. Nevertheless, this approach has certain drawbacks, as tiny remnants of solvents may remain after the process, which can impede adherence to quality standards. Additionally, volatile solvents like methanol and ethanol, which are flammable, need specific precautions to prevent fires.

**Table 3: Common plasticizers used in ODF formulations.**

Plasticizer	Allowed Concentration (w/w %) *Depends on polymer concentration
Glycerin	14-15
Propylene glycol	7-8
Polyethylene glycol 400	7-25
Polyethylene glycol 4000	20-25

#### 4.2. Hot Melt Extrusion

The solvent-casting method was previously used to develop oral thin films. Although this film preparation method allows for flexibility, clarity, uniformity, and the desired thicknesses for more effortless drug loading, it is limited by reduced elasticity and increased tensile strength (Patil et al., 2024).

Another disadvantage of films made through solvent casting techniques is the reliance on organic solvents for many polymers that do not dissolve in water. Residues from organic solvents are difficult to dispose of and can lead to environmental problems, posing hazards (Liu et al., 2012). Pharmaceutical industries needed an alternative method to address these issues, and they discovered that the hot-melt extrusion method offered numerous benefits. There is no requirement for solvents when processing oral films. Furthermore, this approach allows the production of extrudates in one step, eliminating the need to compress drugs and excipients, resulting in cost-effectiveness. Melting active substances and polymers into liquid form and mixing them allows for a consistent spread of particles, enhancing drug availability (Pimparade et al., 2017).

In the past, the hot-melt extrusion technique was utilized to create sustained-release tablets and granules for transmucosal and transdermal drug delivery systems like skin patches (Lakshman et al., 2008). Numerous researchers have cited this technique for producing ODFs. Nevertheless, this technique has become more popular for making ODFs in recent years. This method allows for the easy extrusion of one or multiple drugs to create the desired drug delivery forms. This approach provides

form for drug delivery without the need for the solvent-casting method (Verreck et al., n.d.). Films are produced in the hot melt extruded process by combining the drug, film former, plasticizer, surfactants, and necessary excipients in correct quantities to ensure thorough blending. Following the mixing process, the extrude is transferred to a hopper and then transported to a heated barrel where uniform films are created with less than 1 mm thickness. At times, additional substances are included during the initial processing to guarantee the adherence of films on the mucosal surface (Patil et al., 2024).

In the future, using hot-melt extrusion for film production will allow for the creation of films for gastro-retentive drug delivery and multilayered films for transdermal drug release applications. Hot-melt extrusion techniques can add drugs to catheters and biodegradable stents in medical devices. These viewpoints could boost innovation, research, and commercialization within research institutions, universities, pharmaceutical companies, and biotechnology firms.

#### 4.3. Semi-Solid Casting

The process of semi-solid casting is utilized in the creation of ODFs as well. This technique involves preparing water-soluble solutions and film-forming polymers before incorporating them into the acid-insoluble polymer solution. Plasticizers are mixed in the correct proportions with the pre-made solution to achieve the desired gel mass. The gel mass is carefully cast in controlled conditions to create films with a thickness ranging from 0.015 to 0.05 inches (Ghodake et al., 2013).

#### 4.4. Three-DPrinting Method

for drugs and excipients to be transformed into film

with creating ODFs through a novel method, 3D printing. This method involves adding layers of various ingredients for building, using an additive approach (Cho et al., 2020; El-Say et al., 2022). Scientists have created ODFs with 3D printing methods, and the finished product is formed by solidifying powder, semi-solid, or liquid materials in the final production stage. Extrusion technologies using fused deposition are the most used methods in 3D printing for creating drug delivery systems (Cho et al., 2020). Aripiprazole ODF fabrication is one instance of this technique. At first, aripiprazole filaments are created through hot-melt extrusion, then combined with Polyvinyl alcohol (PVA) and moistened with ethanol before being dried. An extruder is used to create the film filaments. The mixed powder is regularly fed into the die and extruded consistently. The film filament is gathered and then utilized to create 3D-modeled ODFs. The artificial ODFs come in specific sizes in length, width, and depth (Elmeshad & El Hagrasy, 2011).

#### **4.5. Rolling Method**

The rolling method can be used to prepare fast-dissolving films, thus preparing them by rolling drug solution on a drum. The drug is to be dissolved in an alcohol and water mixture. After the rolling of premixed solutions on the roller, the thin film is dried and cut into the desired sizes. The premixed solution comprises the active ingredient, polar solvent, and film-forming polymer, and the required excipients are added to the tank. A controlled valve pump feeds the solution with the intended dose to obtain the desired thickness (Ghodake et al., 2013).

#### **5. Advantages of Fast Dissolving Films**

- Ease of administration to patients who cannot swallow, such as the aged, stroke victims, and bedridden patients; patients who should not swallow, such as renal failure patients; and who refuse to swallow, such as pediatrics, geriatric and psychiatric patients (Preis, 2015).
- Improved compliance.
- Better patient compliance is needed for disabled, bedridden patients and for traveling and busy people who do not have ready access to water (Scarpa et al., 2017).

In recent years, scientists have also experimented

- No chewing needed.
- Better taste.
- Improved stability.
- Allows relatively high drug loading.
- Ability to provide advantages of liquid medication in solid preparation.
- Cost effective.
- Rapid drug therapy intervention.
- Best for patients with oesophageal problems and who have difficulties with deglutition tablets.
- Have acceptable taste and pleasant mouth feeling.
- Leave minimum residue. (Hoffmann et al., 2011)

#### **5.1. Suitable Candidates for Fast-dissolving films**

- The drug should have a pleasant taste.
- The drug to be incorporated should have a low dose of up to 40 mg.
- The drug should have a more minor and moderate molecular weight.
- The drug should have good stability in water as well as saliva.
- It should be partially unionized at the pH of the oral cavity.
- It should be able to permeate the oral mucosal tissue (Kiran Reddy et al., 2018).

## **6. Conclusion**

Fast-dissolving films are an innovative method of delivering drugs orally. It ensures adherence from patients, especially for pediatrics and geriatrics. They can also be utilized in situations where prompt action is necessary. They have numerous benefits compared to traditional forms of medication and are also suitable for individuals with swallowing

- No water needed.

## 7. References

Abdulelah, F. M., & Abdulbaqi, M. R. (2021). Fast dissolving film nanocrystal (FDFN) preparation as a new trend for solubility enhancement of poorly soluble class ii drug tenoxicam. *Archivos Venezolanos de Farmacologia y Terapeutica*, 40(4), 333–339. <https://doi.org/10.5281/zenodo.5218600>

Basu, B., Mankad, A., & Dutta, A. (2022). Methylphenidate Fast Dissolving Films: Development, Optimization Using Simplex Centroid Design and In Vitro Characterization. *Turkish Journal of Pharmaceutical Sciences*, 19(3), 251–266. <https://doi.org/10.4274/tjps.galenos.2021.99223>

Benet, L. Z., Hosey, C. M., Ursu, O., & Oprea, T. I. (2016). BDDCS, the Rule of 5, and drugability. *Advanced Drug Delivery Reviews*, 101, 89–98. <https://doi.org/10.1016/j.addr.2016.05.007>

Bodini, R., Guimarães, J., Monaco, C., & Carvalho, R. (2019). Effect of starch and hydroxypropyl methylcellulose polymers on the properties of orally disintegrating films. *Journal of Drug Delivery Science and Technology*, 51. <https://doi.org/10.1016/j.jddst.2019.03.028>

Centkowska, K., Ławrecka, E., & Sznitowska, M. (2020). The technology of orodispersible polymer films with micronized loratadine—influence of different drug loadings on film properties. *Pharmaceutics*, 12(3). <https://doi.org/10.3390/pharmaceutics12030250>

Cho, H. W., Baek, S. H., Lee, B. J., & Jin, H. E. (2020). Orodispersible polymer films with the poorly water-soluble drug, olanzapine: Hot-melt pneumatic extrusion for single-process 3D printing. *Pharmaceutics*, 12(8), 1–16. <https://doi.org/10.3390/pharmaceutics12080692>

Cilurzo, F., Cupone, I. E., Minghetti, P., Selmin, F., & Montanari, L. (2008). Fast-dissolving films made of maltodextrins. *European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik e.V.*, 70(3), 895–900. <https://doi.org/10.1016/j.ejpb.2008.06.032>

Elmeshad, A. N., & El Hagrasy, A. S. (2011). Characterization and optimization of orodispersible

difficulties, Parkinson's disease, mucositis, or nausea.

mosapride film formulations. *AAPS PharmSciTech*, 12(4), 1384–1392. <https://doi.org/10.1208/s12249-011-9713-z>

El-Say, K. M., Felimban, R., Tayeb, H. H., Chaudhary, A. G., Omar, A. M., Rizg, W. Y., Alnadwi, F. H., Abd-Allah, F. I., & Ahmed, T. (2022). Pairing 3D-Printing with Nanotechnology to Manage Metabolic Syndrome. *International Journal of Nanomedicine*, 17, 1783–1801. <https://doi.org/10.2147/IJN.S357356>

Fink, C., Sun, D., Wagner, K., Schneider, M., Bauer, H., Dolgos, H., Mäder, K., & Peters, S.-A. (2020). Evaluating the Role of Solubility in Oral Absorption of Poorly Water-Soluble Drugs Using Physiologically-Based Pharmacokinetic Modeling. *Clinical Pharmacology and Therapeutics*, 107(3), 650–661. <https://doi.org/10.1002/cpt.1672>

*GENERAL NOTICES AND REQUIREMENTS.* (n.d.).

[https://doi.org/10.31003/USPNF\\_M99989\\_09\\_01](https://doi.org/10.31003/USPNF_M99989_09_01)

Ghodake, P., Karande, K., Osmani, R., Bhosale, R., Harkare, B., & Kale, B. (2013). Mouth Dissolving Films: Innovative Vehicle for Oral Drug Delivery. *International Journal of Pharma and Bio Sciences*, 2, 41–47.

Hamza, M. (2017). Development and Evaluation of Orodispersible Films of Lamotrigine: Hydroxypropyl B Cyclodextrin Inclusion Complex. *Al-Azhar Journal of Pharmaceutical Sciences*, 56(2), 31–46. <https://doi.org/10.21608/ajps.2017.28458>

Hoffmann, E. M., Breitenbach, A., & Breitreutz, J. (2011). Advances in orodispersible films for drug delivery. *Expert Opinion on Drug Delivery*, 8(3), 299–316. <https://doi.org/10.1517/17425247.2011.553217>

Irfan, M., Rabel, S., Bukhtar, Q., Qadir, M. I., Jabeen, F., & Khan, A. (2016). Orally disintegrating films: A modern expansion in drug delivery system. *Saudi Pharmaceutical Journal: SPJ: The Official Publication of the Saudi Pharmaceutical Society*, 24(5), 537–546. <https://doi.org/10.1016/j.jsps.2015.02.024>

Javeer, S. D., & Amin, P. D. (2014). Solubility and dissolution enhancement of HPMC - based solid

technique. *Asian Journal of Pharmaceutics*, 8(2), 119–124. <https://doi.org/10.4103/0973-8398.134950>

Juliano, C., Cossu, M., Pigozzi, P., Rassa, G., & Giunchedi, P. (2008). Preparation, In Vitro Characterization and Preliminary In Vivo Evaluation of Buccal Polymeric Films Containing Chlorhexidine. *AAPS PharmSciTech*, 9, 1153–1158. <https://doi.org/10.1208/s12249-008-9153-6>

Karolewicz, B. (2016). A review of polymers as multifunctional excipients in drug dosage form technology. *Saudi Pharmaceutical Journal*, 24(5), 525–536. <https://doi.org/https://doi.org/10.1016/j.jsps.2015.02.025>

Kiran Reddy, U., Sunil, K., Reddy, K., Katta, M., & K, T. (2018). *A DETAILED REVIEW ON FAST DISSOLVING ORAL FILMS*.

Koland, M., Sandeep, V., & Charyulu, N. (2010). Fast Dissolving Sublingual Films of Ondansetron Hydrochloride: Effect of Additives on in vitro Drug Release and Mucosal Permeation. *Journal of Young Pharmacists : JYP*, 2(3), 216–222. <https://doi.org/10.4103/0975-1483.66790>

Kulkarni, A., H.A, D., & M, M. (2010). Exploration of different polymers for use in the formulation of oral fast dissolving strips. *Journal of Current Pharmaceutical Research*, 2.

Lakshman, J. P., Cao, Y., Kowalski, J., & Serajuddin, A. T. M. (2008). Application of melt extrusion in the development of a physically and chemically stable high-energy amorphous solid dispersion of a poorly water-soluble drug. *Molecular Pharmaceutics*, 5(6), 994–1002. <https://doi.org/10.1021/mp8001073>

Liew, K. Bin, Tan, Y. T. F., & Peh, K. K. (2014). Effect of polymer, plasticizer and filler on orally disintegrating film. *Drug Development and Industrial Pharmacy*, 40(1), 110–119. <https://doi.org/10.3109/03639045.2012.749889>

Lin, S.-Y. Y., Lee, C.-J. J., & Lin, Y.-Y. Y. (1995). Drug-polymer interaction affecting the mechanical properties, adhesion strength and release kinetics of piroxicam-loaded Eudragit E films plasticized with different plasticizers. *Journal of Controlled Release*, 33(3), 375–381. <https://doi.org/10.1016/0168->

Liu, X., Lu, M., Guo, Z., Huang, L., Feng, X., & Wu, C. (2012). Improving the chemical stability of amorphous solid dispersion with cocrystal technique by hot melt extrusion. *Pharmaceutical Research*, 29(3), 806–817. <https://doi.org/10.1007/s11095-011-0605-4>

Lou, J., Duan, H., Qin, Q., Teng, Z., Gan, F., Zhou, X., & Zhou, X. (2023). Advances in Oral Drug Delivery Systems: Challenges and Opportunities. *Pharmaceutics*, 15(2). <https://doi.org/10.3390/pharmaceutics15020484>

Maher, E. M., Ali, A. M. A., Salem, H. F., & Abdelrahman, A. A. (2016). In vitro/in vivo evaluation of an optimized fast dissolving oral film containing olanzapine co-amorphous dispersion with selected carboxylic acids. *Drug Delivery*, 23(8), 3088–3100. <https://doi.org/10.3109/10717544.2016.1153746>

Milligan, J. J., & Saha, S. (2022). A Nanoparticle's Journey to the Tumor: Strategies to Overcome First-Pass Metabolism and Their Limitations. *Cancers*, 14(7). <https://doi.org/10.3390/cancers14071741>

Mishra, R., & Amin, A. (2011). Formulation and Characterization of Rapidly Dissolving Films of Cetirizine hydrochloride using Pullulan as a Film Forming Agent. *Indian Journal of Pharmaceutical Education and Research*, 45, 71–77.

Parejiya, P., Patel, R., Mehta, D., Shelat, P., & Barot, B. (2013). Quick dissolving films of nebiivolol hydrochloride: Formulation and optimization by a simplex lattice design. *Journal of Pharmaceutical Investigation*, 43. <https://doi.org/10.1007/s40005-013-0080-5>

Pathak, K., & Raghuvanshi, S. (2015). Oral Bioavailability: Issues and Solutions via Nanoformulations. In *Clinical Pharmacokinetics* (Vol. 54, Issue 4, pp. 325–357). Springer International Publishing. <https://doi.org/10.1007/s40262-015-0242-x>

Patil, H., Vemula, S. K., Narala, S., Lakkala, P., Munnangi, S. R., Narala, N., Jara, M. O., Williams, R. O., Terefe, H., & Repka, M. A. (2024). Hot-Melt Extrusion: from Theory to Application in Pharmaceutical Formulation—Where Are We Now? *AAPS PharmSciTech*, 25(2), 37. <https://doi.org/10.1208/s12249-024-02749-2>



3659(94)00109-8

- Pechová, V., Gajdziok, J., Muselík, J., & Vetchý, D. (2018). Development of Orodispersible Films Containing Benzydamine Hydrochloride Using a Modified Solvent Casting Method. *AAPS PharmSciTech*, 19(6), 2509–2518. <https://doi.org/10.1208/s12249-018-1088-y>
- Pichayakorn, W., Suksaeree, J., Boonme, P., Amnuait, T., Taweepreda, W., & Ritthidej, G. C. (2013). Deproteinized natural rubber film forming polymeric solutions for nicotine transdermal delivery. *Pharmaceutical Development and Technology*, 18(5), 1111–1121. <https://doi.org/10.3109/10837450.2012.705297>
- Pimparade, M. B., Vo, A., Maurya, A. S., Bae, J., Morott, J. T., Feng, X., Kim, D. W., Kulkarni, V. I., Tiwari, R., Vanaja, K., Murthy, R., Shivakumar, H. N., Neupane, D., Mishra, S. R., Murthy, S. N., & Repka, M. A. (2017). Development and evaluation of an oral fast disintegrating anti-allergic film using hot-melt extrusion technology. *European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik e.V.*, 119, 81–90. <https://doi.org/10.1016/j.ejpb.2017.06.004>
- Pollastri, M. (2010). Overview on the Rule of Five. *Current Protocols in Pharmacology / Editorial Board, S.J. Enna (Editor-in-Chief) ... [et Al.], Chapter 9, Unit 9.12.* <https://doi.org/10.1002/0471141755.ph0912s49>
- Preis, M. (2015). Orally Disintegrating Films and Mini-Tablets—Innovative Dosage Forms of Choice for Pediatric Use. In *AAPS PharmSciTech* (Vol. 16, Issue 2, pp. 234–241). Springer New York LLC. <https://doi.org/10.1208/s12249-015-0313-1>
- Rédai, E. M., Antonoaea, P., Todoran, N., Vlad, R. A., Bîrsan, M., Tătaru, A., & Ciurba, A. (2021). Development and evaluation of fluoxetine fast dissolving films: An alternative for noncompliance in pediatric patients. *Processes*, 9(5). <https://doi.org/10.3390/pr9050778>
- Reveny, J., Tanuwijaya, J., & Remalya, A. (2017). Formulation of Orally Dissolving Film (ODF) Metoclopramide Using Hydroxy Propyl Methyl Cellulose and Polyvinyl Alcohol with Solvent Casting Method. *International Journal of ChemTech Research*, 10(1), (316-321).
- Different Approaches, a Review. *Polymers*, 14(16). <https://doi.org/10.3390/polym14163318>
- Sareen, S., Mathew, G., & Joseph, L. (2012). Improvement in solubility of poor water-soluble drugs by solid dispersion. *International Journal of Pharmaceutical Investigation*, 2(1), 12–17. <https://doi.org/10.4103/2230-973X.96921>
- Savjani, K. T., Gajjar, A. K., & Savjani, J. K. (2012). Drug solubility: importance and enhancement techniques. *ISRN Pharmaceutics*, 2012, 195727. <https://doi.org/10.5402/2012/195727>
- Scarpa, M., Stegemann, S., Hsiao, W. K., Pichler, H., Gaisford, S., Bresciani, M., Paudel, A., & Orlu, M. (2017). Orodispersible films: Towards drug delivery in special populations. In *International Journal of Pharmaceutics* (Vol. 523, Issue 1, pp. 327–335). Elsevier B.V. <https://doi.org/10.1016/j.ijpharm.2017.03.018>
- Sevinç Özakar, R., & Özakar, E. (2021). Current overview of oral thin films. *Turkish Journal of Pharmaceutical Sciences*, 18(1), 111–121. <https://doi.org/10.4274/tjps.galenos.2020.76390>
- Shahiwala, A. (2011). Formulation approaches in enhancement of patient compliance to oral drug therapy. *Expert Opinion on Drug Delivery*, 8(11), 1521–1529. <https://doi.org/10.1517/17425247.2011.628311>
- Singh, H., Singla, Y. P., Narang, R. S., Pandita, D., Singh, S., & Narang, J. K. (2018). Frovatriptan loaded hydroxy propyl methyl cellulose/treated chitosan based composite fast dissolving sublingual films for management of migraine. *Journal of Drug Delivery Science and Technology*, 47, 230–239. <https://doi.org/10.1016/j.jddst.2018.06.018>
- Srebro, J., Brniak, W., & Mendyk, A. (2022). Formulation of Dosage Forms with Proton Pump Inhibitors: State of the Art, Challenges and Future Perspectives. *Pharmaceutics*, 14(10). <https://doi.org/10.3390/pharmaceutics14102043>
- Verreck, G., Six, K., Van Den Mooter, G., Baert, L., Peeters, J., & Brewster, M. E. (n.d.). *Characterization of solid dispersions of itraconazole and hydroxypropylmethylcellulose prepared by melt extrusion\*/ part I.* [www.elsevier.com/locate/ijpharm](http://www.elsevier.com/locate/ijpharm)

Salawi, A. (2022). Pharmaceutical Coating and Its

Vishvakarma, P. (2018). Design and development of montelukast sodium fast dissolving films for better therapeutic efficacy. *Journal of the Chilean Chemical Society*, *63*(2), 3988–3993. <https://doi.org/10.4067/s0717-97072018000203988>

Vuddanda, P. R., Montenegro-Nicolini, M., Morales, J. O., & Velaga, S. (2017). Effect of plasticizers on the physico-mechanical properties of pullulan based pharmaceutical oral films. *European Journal of Pharmaceutical Sciences*, *96*, 290–298. <https://doi.org/10.1016/j.ejps.2016.09.011>