

Enhancing Bioavailability of Phytoconstituents Using Fast-Dissolving Films: A Comprehensive Review

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Abstract

It has long been known that phytoconstituents have a wide range of medicinal applications and can provide safer, less harmful substitutes for manufactured medications. However, poor oral bioavailability which results from low water solubility, poor permeability, gastrointestinal tract instability, and significant first-pass metabolism seriously restricts their therapeutic value. In order to solve these biopharmaceutical issues, fast dissolving films, or FDFs, have become a revolutionary platform. An extensive summary of the use of FDFs to improve the bioavailability of phytoconstituents is given in this review. We go over the basic difficulties in delivering phytoconstituents, the anatomical and physiological underpinnings of improved absorption through the oral cavity, formulation strategies, including the choice of polymers and cutting-edge methods like the integration of nanotechnology, and essential quality characteristics for film performance. Recent developments, case studies of effective phytoconstituent-loaded FDFs, regulatory issues, and future prospects are also highlighted in the study. FDFs provide a paradigm change in the efficient administration of bioactive plant-derived substances by providing a patient-centric, quickly dissolving dosage form that avoids gastrointestinal degradation and first-pass metabolism.

Keywords: Fast dissolving films, oral thin films, phytoconstituents, bioavailability, buccal delivery, herbal formulations, nanotechnology, taste masking

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Introduction

From the early days, herbal drugs were used as medicines [1,2]. Such herbal drugs could be either single bioactive compounds, enriched fraction or multiconstituent herbal extracts. Secondary metabolites are the predominant type of phytoconstituents that prevent, treat and mitigate diseases. Multiconstituent herbal drugs are time tested, effective and safe. However, eventually, the use of single drug therapies or bioactive compounds substituted multiconstituent herbal medicines of traditional medical systems [3]. Plants represent a valuable resource for lead compound discovery for current medicine as they possess enormous chemical diversities [4–6]. As a general practice, multiconstituent herbal extracts or enriched fractions rather than isolated bioactives are used as medicines since there is synergy between different phytoconstituents [7,8]. Synergy exists because of the presence of multitarget activities of different phytoconstituents in the same extract or enriched fraction, better physicochemical/pharmacokinetics of

phytoconstituents in the presence of different phytoconstituents, modulation of resistance mechanisms through different phytoconstituents and decreased toxicity through the interaction of different phytoconstituents [9]. In addition, multiconstituent herbal extracts and enriched fractions are advantageous over isolated bioactives due to the difficulty in obtaining pure bioactives, loss of biological activity after isolation of bioactives, lack of knowledge on bioactives/phytoconstituents and chemical instability of phytoconstituents [10].

The utilization of phytoconstituents, that is, the biologically active constituents present in plants, has been an integral part of the traditional medicines practiced across different parts of the world for many centuries [1,2]. The increasing knowledge of the side effects of synthetic drugs and the subsequent growing demand for safe and potent remedies have prompted a paradigm shift towards natural products over the past few decades [5,6]. Some of the common actions of phytoconstituents, which include flavonoids,

alkaloids, terpenes, polyphenols, and glycosides, among others, are antioxidant, anti-inflammatory, antibacterial, anticancer, hepatoprotective, and neuroprotective [10–12].

Nonetheless, one of the key issues that have hindered the development of phytoconstituents as potent pharmaceutical agents is their poor oral bioavailability [13,14]. This is primarily because most phytoconstituents tend to be large in size, poorly soluble in aqueous media, permeable across biological barriers, unstable under the acidic conditions of the stomach, susceptible to enzymatic degradation, and prone to first-pass metabolism by the liver enzymes [12,15,16]. As a result, such substances do not absorb well after oral administration in the form of tablets or capsules, leading to their low blood levels and poor pharmacological activity [17].

Phytoconstituents often fall under Class II (poorly soluble, highly permeable) and Class IV (poorly soluble, poorly permeable) drugs according to the Biopharmaceutics Classification System (BCS) [18,19], hence the difficulties in formulating such drugs. Some of the methods that have been developed to improve the efficacy of phytoconstituents as medicinal agents include solid dispersions, liposomes, nanoparticles, and self-emulsifying drug delivery systems [20,21]. One of the promising techniques that has emerged is the use of fast-dissolving films (FDFs) or oral thin films (OTFs) [22,23].

Currently, the oral route is one of the most extensively used drug delivery systems [24]. The use of this route offers some significant benefits compared to other routes of administration. However, oral formulations should be improved because of some disadvantages associated particularly with certain categories of patients, such as the elderly population, children, and patients suffering from dysphagia having different diseases due to their inability to chew or swallow orally administered formulations [25]. Due to the risk of choking, many elderly and children patients tend to avoid swallowing conventional solid drugs. Moreover, the resemblance of oral formulations to tablets may result in choking even after consuming rapidly dissolving tablets. One study found that 26% out of 1,576 participants had problems with swallowing drugs [26]. The main factors causing problems with swallowing pills included their sizes, Flavors, and geometrical characteristics. Elderly and young patients and people travelling and lacking water access showed more problems in taking pills [27].

In order to resolve the problem associated with swallowing tablets and other solid formulations, fast-dissolving drug delivery systems were created in the late 1970s as an alternative to conventional tablets, capsules, and syrups [28]. In this regard, it is necessary to note that fast-dissolving drug delivery systems

involve the usage of solid dosage forms dissolving instantly in the mouth without water [27]. The types of fast-dissolving formulations have been expanded from the traditional tablets or capsules to modified-release formulations, ODTS, and more modern ODFDs [29,30].

When FDFs come into contact with saliva, they break down quickly usually in a matter of seconds to several minutes releasing the medicine that has been integrated for absorption through the oral mucosa [22,31,32].

This delivery system offers several distinct advantages for phytoconstituents:

- (1) Bypassing first-pass metabolism through direct absorption into the systemic circulation via the highly vascularized buccal and sublingual mucosa [33,34]
- (2) Avoiding gastrointestinal degradation
- (3) Providing rapid onset of action
- (4) Offering patient-friendly administration without the need for water or swallowing
- (5) Enabling precise dosing.

The purpose of this paper is to give a thorough overview of the use of FDFs to increase phytoconstituent bioavailability. We go on the anatomical underpinnings of buccal absorption, the biopharmaceutical difficulties associated with phytoconstituents, formulation strategies, including advanced processes and polymer selection, important quality aspects, current case studies, and future prospects.

2. Biopharmaceutical Challenges of Phytoconstituents to overcome

The naturally occurring bioactive molecules obtained from the medicinal plants are called phytoconstituents, and they are flavonoids, polyphenols, alkaloids, terpenoids, glycosides, lignans, tannins, saponins and phenolic acids [10,11]. These compounds have been found to have a wide range of pharmacological properties such as antioxidant, anti-inflammatory, antimicrobial, antidiabetic, anticancer, hepatoprotective, cardioprotective and neuroprotective properties. Although phytoconstituents have proven to be highly potent in preclinical studies, the translation to the clinical setting of many of these compounds has been limited by inadequate biopharmaceutical properties [15,16]. Most phytoconstituents are poorly soluble in water, do not cross biological membranes easily, are not stable in the gastrointestinal tract, undergo high first pass metabolism, have rapid systemic elimination and are subject to efflux via membrane transporters. The restrictions strongly affect the oral bioavailability, which leads to insufficient levels in plasma and variable therapeutic efficacy [13]. Therefore, the enhancement of biopharmaceutical properties of

phytoconstituents is a central theme in the pharmaceutical research, and new drug delivery systems, including phytosomes, liposomes, polymeric nanoparticles, nanoemulsions, solid lipid nanoparticles, nanostructured lipid carriers and self-emulsifying drug delivery systems have been developed [14,17,21].

Poor Aqueous Solubility

One of the major problems affecting the oral bioavailability of phytoconstituents is their poor aqueous solubility [35,36]. Compounds with low water solubility dissolve slowly in gastrointestinal fluids which reduces the concentrations available for gastrointestinal absorption; therefore, dissolution is a prerequisite to gastrointestinal absorption [18,19]. Many of the phytochemicals that have therapeutic value have large aromatic systems and hydrophobic molecules which often lead to poor water solubility [15]. These include curcumin, resveratrol, quercetin, naringenin, luteolin, apigenin, kaempferol, and silybin. For example, curcumin, which is one of the most active pharmacologically, is poorly soluble in water (a few micrograms per millilitre) and has very low oral bioavailability [37,38]. On the other hand, if it does not dissolve adequately, the drug is not absorbed, it takes longer to have an effect, there is more inter-individual variability and larger oral doses are required to produce therapeutic results. Unfortunately, poorly water-soluble medicaments remain a challenging, but important, class of pharmaceutical products to manage a wide variety of disease [20,39]. They remain commonly found in discovery and improvements are typically limited by the lack of a full understanding of the compound, physiological and bio-chemical changes which occur during administration and absorption and how these changes affect bio-availability separately and in combination. In the first stage of the selection process, many drugs pass high through-put screening but due to lack of aqueous solubility, they encounter attrition in later stages of development [35,36]. Most of the poorly aqueous soluble drugs are unable to dissolve in the available number of gastrointestinal juices. It is eminent that these kinds of drugs show limited dissolution kinetics and poor bioavailability. Different types of formulation strategies for improving the water solubility of drugs include solid dispersion, lipid formulation, cyclodextrin complexes and nanocrystal formation [39–41]. Co-crystal formation, and salt formation. Solid dispersion (SD) is a promising technique having the ability to generate and sustain supersaturation, results in an improved bioavailability of drugs [42].

Most phytoconstituents have very poor water solubility and are lipophilic in nature [15]. One of the main things preventing them from dissolving in

gastrointestinal fluids is their hydrophobicity, which lowers the concentration that may be absorbed. The water solubility of a few phytoconstituents is shown in Table 1 [19,43].

Phytoconstituent	Source	BCS Class
Curcumin	Curcuma longa	IV
Quercetin	Sophora japonica	II
Resveratrol	Vitis vinifera	II
Silymarin	Silybum marianum	II/IV
Piperine	Piper nigrum	II
Berberine	Berberis aristata	III/IV

Table 1: Aqueous Solubility of

Common Phytoconstituents

Poor Permeability

Most drugs are absorbed mainly in the upper portions of the GI tract, the duodenum and jejunum, after oral administration [44]. However, the stomach is less able to absorb drugs because its surface area is smaller and the mucous lining is thicker. A drug will have to cross several barriers to be absorbed from the GI lumen into the epithelium, mucosa and blood or lymph capillaries: the gastric juice, the pericellular matrix, and the mucus-rich layer. The intestinal mucosal barrier is comprised of microvilli on the luminal side and then epithelia attached to a basement membrane in the lamina propria. The lamina propria is the site of nerves, blood vessels and lymph vessels under the epithelial cells. Drug molecules can cross these barriers in various ways such as: between adjacent cells (paracellular transport), through the cell membrane (transcellular transport), by carrier mediated uptake, or by transcytosis as illustrated in Fig.1 [45,46]. It is known that transcellular route is the main path for the uptake of small molecule drugs [44]. This is done by diffusion across the cell membrane from the area of high concentration (e.g. GI fluid) to low concentration (e.g. blood stream). The rate of diffusion is directly proportional to the concentration gradient but other factors include the degree of ionization, molecular size, surface area for absorption and lipophilicity of the drug. The cell membrane is

lipophilic, meaning that the more lipophilic the drug molecule, the faster it moves into the cell. Besides the lipophilicity, drugs with a smaller molecular weight have a quicker translocation of cells compared to those of higher molecular weight. Paracellular transport involves the uptake of drug molecules by diffusion and convective volume flow through the intercellular spaces filled with water. The absorption pathway is normally not very efficient, however, because most drug molecules are not able to pass freely between the cells of the intestinal membrane due to the tight junctions present between the cells, which have a pore diameter of 4 to 8 Å [47]. The paracellular transport is tightly regulated by the tight junctions, which are the main barrier to the permeation of ions and larger molecules. In addition, only 0.1%-0.01% of the total surface area of the intestinal membranes is covered by this pathway and its accessibility decreases from the jejunum to the colon even further, reducing the possibility for drug absorption [45,47]. Many studies have been carried out to modify the physicochemical properties of drugs and to modify the barrier characteristics to improve drug delivery across these barriers. This has been accomplished through a chemical modification of a drug molecule and/or by optimizing the formulation design [36].

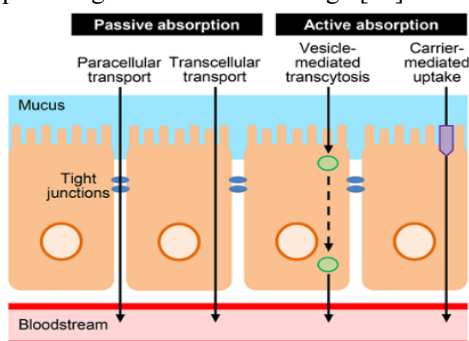


Figure 2 Schematic illustration of drug absorption and transport through the intestinal epithelium. After dispersion into the mucosal layer, drugs can be absorbed passively (via a paracellular or transcellular route) or actively (via vesicle-mediated transcytosis or carrier-mediated uptake).

Gastrointestinal Instability

One of the significant biopharmaceutical challenges to oral bioavailability of phytoconstituents is gastrointestinal (GI) instability [12,15]. The gastrointestinal tract environment of the body, characterized by acidic gastric pH, gastrointestinal enzymes, bile salts, fluctuation of gastrointestinal pH, and gastrointestinal flora, poses severe physiological stresses and challenges to phytoconstituents after oral administration. These can cause chemical degradation, hydrolysis, oxidation or enzymatic metabolism of the phytoconstituents before they get to the point of absorption in the small intestine [12,48]. This results in the concentration of the bioactive compound available for absorption is greatly diminished, thereby

resulting in poor systemic exposure and a reduced therapeutic efficacy. A considerable number of phytoconstituents, such as polyphenols and flavonoids, are chemically unstable in a gastrointestinal environment. For instance, curcumin is sensitive to degradation in the alkaline environment of the intestine, and epigallocatechin gallate (EGCG) can oxidize in the intestinal environment [49,50]. Likewise, anthocyanins are prone to degradation at neutral and alkaline pH, which leads to structural changes and bioinactivity [51]. Further, gut microbiota and enzymes can convert the phytoconstituents to inactive or less active metabolites before absorption [48]. This presystemic degradation leads to a significant reduction in the proportion of the orally administered dose reaching systemic circulation. In order to overcome gastrointestinal instability, several formulation strategies have been investigated, such as: phytosomes, liposomes, polymeric nanoparticles, Solid-lid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), fast dissolving oral film (FDOF) and self-emulsifying drug delivery systems (SEDDS) [13]. These advanced delivery systems prevent the degradation of phytoconstituents by acidic pH, enzymes and oxidation and enhance the stability, intestinal absorption, and the oral bioavailability. Of these, phytosomes have exhibited significant potential as they are a complex formed by a phospholipid barrier that protects the phytoconstituent, making it more stable during gastrointestinal passage and, thus, more efficiently absorbed across the epithelial layer of the gastrointestinal tract [21,52].

Large Doses and Taste Issues

The low aqueous solubility, low intestinal permeability, instability in the gastrointestinal tract, and high levels of first-pass metabolism are responsible for the low oral bioavailability of many phytoconstituents. This means that only a small portion of the drug gets into the bloodstream. Relatively high oral doses are sometimes needed to obtain therapeutic plasma level. When administered at high doses, however, the potential for gastrointestinal discomfort may be greater, patient adherence may be lower, formulations may be larger and the cost of treatment may be higher. For instance, curcumin has strong anti-inflammatory and antioxidant properties, but is poorly bioavailable from oral administration (only 1% available) and requires gram doses in many clinical trials [37,38]. Likewise, the therapeutic effects of quercetin and resveratrol are not seen until higher doses are used due to low bioavailability in the systemic circulation [53–55]. Such restrictions have led to the use of more sophisticated delivery methods like phytosomes, liposomes or nanoparticles, which increase bioavailability but do not require high therapeutic doses [13]. The other major problems with

phytoconstituents is their bitter, astringent and sometimes pungent taste [56]. The sensory characteristics occur due to the presence of polyphenols, alkaloids, tannins and terpenoids in the mouth that interact with the taste receptors [57,58]. For example, tannin rich extracts have a very astringent taste while some alkaloids are bitter, and catechins and quercetin have a very bitter flavor [58]. The overall organoleptic characteristics are not desirable and affect both patient acceptance and patient compliance particularly in paediatric and geriatric patients, and can affect successful formulation of oral dosage forms [59,60]. Palatability has been extensively studied by the use of taste-masking techniques such as microencapsulation, the formation of phytosomes, utilisation of lipid-based carriers, polymer coating, cyclodextrin inclusion complexes and flavouring agents, with the aim of keeping the therapeutic properties intact [61–63].

Key taste problems and their causes

Bitter taste

- Large groups of phytochemicals (polyphenols, flavonoids, saponins, alkaloids, glucosinolates, isoflavones, phytoalexins) frequently activate human bitter receptors (TAS2Rs) [57,58]
- Examples: flavonoids in fruits and juices, saponins and phenolics in pulses and pea protein, glucosinolates in Brassicaceae, isoflavones in soy, bitter polyphenols in basil and beer [56].
- Many healthy “phytonutrients” in vegetables, fruits, oils, and herbs are inherently bitter or acrid, historically treated as toxins and often bred or processed out of foods [56].

Approaches to manage taste issues

Strategy	How it helps with taste
Encapsulation / powders	Masks bitterness/off-flavour, enables use of bitter extracts in beverages
Flavour & sweetener design	Fruity/other notes can mask bitterness, metallic and astringent aftertastes
Breeding & selection	Adjusts specific bitter/astringent phytochemicals rather than total content

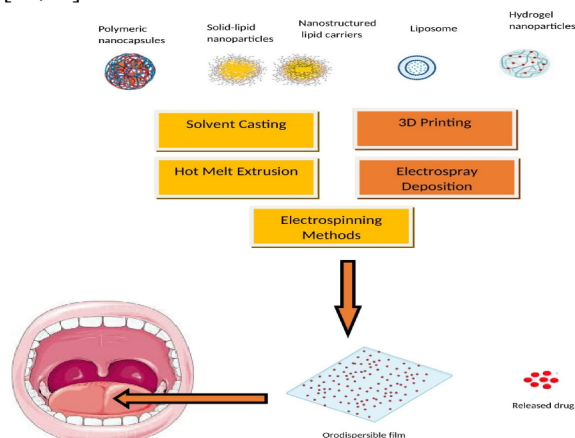
Bitter receptor antagonists/masking compounds	Block TAS2R activation (e.g., from allspice)
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3. Fast Dissolving Oral Films: An Overview

The oral route is still the most popular for drug delivery because of how simple it is to use and increased patient compliance [24]. Drugs can have different oral bioavailability depending on physical and chemical characteristics and physiological conditions of the GI tract. Further, most oral drugs experience first-pass metabolism [64]. Fast-dissolving tablets (FDTs) were created late in the 1970s to help elderly and pediatric patients who have trouble gulping pills in the form of pills [27,28]. The tablets are formulated with super disintegrant and hydrophilic ingredients for the enhancement of the bioavailability, rapid effect and patient compliance. Many FDTs are prepared by the lyophilization process, which is expensive, and sometimes difficult to handle, transport and store as they can become fragile and friable [28]. Also Choking fear on fast dissolving tablet. Oral fast-dissolving films (OFDFs) are a new drug delivery system which disintegrates quickly in the mouth without the need to chew or swallow water [22,23]. These can offer a number of advantages, such as improved bioavailability, dosing accuracy, patient acceptability, flexibility for drug formulations, concealed delivery, stability, mobility and suitability across a variety of patient groups [30,32].

To avoid the issues of fast dissolving tablets, it might be possible to use a film that will dissolve quickly. Fast dissolving tablets may have drawbacks which can be overcome with OFDFs, which look like ultra-thin strips [22,31]. The film formulation is made of polymers, active pharmaceutical ingredients (APIs), plasticizers, saliva-stimulating agents, sweetening agents, flavors, preservatives and colors [29,31]. Easy to operate and quickly moisten the mucous membranes of the patient's mouth. They are better than the conventional oral dose forms due to their easy administration, rapid digestion and palatability, which in turn increases patient adherence, especially in children, elderly patients, and other sensitive populations [25]. This could also increase the efficiency of drug delivery and quicker drug effect. The drug is released for Oro mucosal absorption as soon as the film dissolves after adhering to the application site and hydrating. The film can be modified to allow for gastrointestinal absorption when ingested. The permeability and blood flow of the oral mucosa are 4 to 1,000 times greater than that of skin, which allows drugs to be absorbed and are more bioavailable [65,66]. OPDF is an innovative way to provide improved consumer acceptance due to its fast-

dissolving properties and self-administration without chewing or water. With its convenient packaging, easy administration, ability to eradicate bad taste, and ease of use, the film is a successful fast-dissolving medication administration via intraoral technology that meets market demands. The film is stuck on the top or bottom of the tongue. For either local or systemic absorption, it sticks to the application site and releases the active ingredient fast. This rapid dissolving film could open up new markets for several types of medicines, such as neuroleptics, cardiovascular medicines, anaesthetic, antiallergy and anti-asthmatic drugs and erectile function stimulants [22,32]. Many types of medicines could be formulated as films that dissolve in the mouth. Therapeutic applications for creative products encompass pediatric (anti-tussive, expectorant, antihistamines), geriatric (antiepileptic, expectorant) and gastrointestinal disease, pain (migraine) and anti-Parkinson therapy [67,68].



Key Features and Advantages

- **Rapid disintegration:** Typically, within 30–60 seconds for fast types, driven by hydrophilic polymers such as HPMC, pullulan, maltodextrin, and others [69,70].
- **Improved bioavailability:** Bypass part of first-pass metabolism via buccal/sublingual absorption; useful for BCS class II/IV and high first-pass drugs (e.g., meloxicam, rosuvastatin, promethazine [34,64]).
- **Patient convenience:** No water, low choking risk, precise dosing, good for pediatric, geriatric, dysphagic, bedridden, and psychiatric patients [23,25].

Types and release Patterns

Film types	Disintegrating/release behaviour	Typical use
Fast/flash ODF	<30–60 s, immediate release	Acute symptom

		s, rapid onset
Moderately/slow ODF	1–30+ min	e.g., nicotine, sustained buccal action
Dual / prolonged systems	Fast disintegration, but matrix/NPs give prolonged release (hours)	Where extended plasma levels needed

Anatomical Basis for Enhanced Absorption

For medications that are poorly absorbed through the gastrointestinal tract, the oral mucosa offers an optimal absorption location [33,66]. The sublingual (floor of the mouth) and buccal (cheek) regions are distinguished by:

- **“High vascularization”** Oral mucosa is “well-vascularized,” and drugs absorbed via buccal mucosa bypass the liver’s metabolic pathway and reach systemic circulation directly [71,72]. Venous drainage from buccal/sublingual regions goes to the internal jugular/superior vena cava, allowing avoidance of hepatic first-pass metabolism and GI degradation [73,74].
- **“Thin epithelium”** Non-keratinized sublingual epithelium is 100–200 µm thick and 8–12 cell layers; buccal epithelium is thicker (500–800 µm, 40–50 layers) but still relatively permeable [65,75]. In oral cavity permeability models, these thinner non-keratinized regions are specifically cited as “more permeable and particularly suited for systemic drug delivery [34,66]”
- **“Bypass of first-pass metabolism”** By avoiding the hepatic portal circulation and first-pass metabolism entirely, medications taken through the oral mucosa reach the systemic circulation through the facial, lingual, and internal jugular veins [64].
- **“Neutral pH”** The oral cavity has a relatively neutral pH $\approx$ 6.2–7.4 with limited enzymatic activity; this supports drug

stability and is highlighted as a key advantage over GI delivery [71,76].

4. Formulation Strategies for Phytoconstituent Loaded FDFs

Plant-derived actives (flavonoids, polyphenols, alkaloids, complex extracts) pose challenges such as low solubility, bitterness, and limited loading, so FDF/ODF design must be tailored to both the film and the phytoconstituent [17].

Polymers are the backbone of FDFs, determining the mechanical properties, disintegration time, and drug release profile. For phytoconstituents, polymer selection must also consider compatibility with natural extracts and the ability to incorporate taste-masking agents [69,70].

Choice of Film-Forming System and Excipients

- **Hydrophilic polymers:** HPMC, HPC, PVA, pectin, sodium CMC, pullulan and blends (e.g., HPMC + carbomer, HPMC E5 + SCMC) provide rapid disintegration and acceptable mechanics for herbal and algal extracts [69,77].
- **Plasticizers:** Glycerol, PEG 400, propylene glycol optimize flexibility and folding endurance for herbal films (Pongamia, Calendula, Uncaria) [77,78].
- **Organoleptic tailoring:** Sweeteners (sucralose, sorbitol) and Flavors effectively mask the often bitter/astringent taste of polyphenol-rich extracts [56,79].
- **Stabilizers/antioxidants:** Ascorbic acid and appropriate packaging support stability of oxidation-sensitive phytochemicals [50,51].

Taste Masking Strategies

Taste masking is particularly critical for phytoconstituent-loaded FDFs, as most herbal extracts are intensely bitter [56,59]. Effective strategies include:

- **Complexation and Molecular Level Masking:** Donepezil-HP- β -cyclodextrin complexes in ODFs greatly improved palatability versus plain drug films while remaining bioequivalent; masking arises from moderate drug-CD interaction that breaks in gastric acid to allow absorption [40]. Cyclodextrins and maltodextrins similarly reduced dimenhydrinate bitterness in ODFs, confirmed by dual electronic-tongue systems [79,80].
- **Ion-exchange resins:** These resins bind drug molecules, preventing interaction with taste receptors until disintegration in the oral cavity [61,62].

- **Polymer coating:** Coating drug particles with taste-masking polymers such as Eudragit E or ethyl cellulose [61,63].
- **Sweeteners and Flavors:** High-intensity sweeteners (e.g., sucralose, aspartame) and Flavors (mint, licorice, fruit) are the first line of masking and can significantly reduce bitterness, though often insufficient for very bitter APIs. Mixtures of sweeteners and Flavors outperform single agents for masking bitter drugs in fast dissolving films [59,60,79].

Advanced Strategies: Nanotechnology Integration

To overcome the limitations of low drug loading and poor solubility of phytoconstituents, researchers have increasingly explored the integration of nanotechnology with FDF technology [13,17]. This synergistic approach involves incorporating phytoconstituents into nanoparticles before embedding them into the film matrix [81].

1. Nanosuspension and Nanoparticle Loaded Films

- Poorly soluble drugs (paroxetine, nitrendipine, repaglinide, febuxostat, dutasteride, ticagrelor, buspirone) are first turned into nanosuspensions/nanoparticles, then cast into films [20,81].
- Outcomes:
 - Large increases in dissolution (e.g., febuxostat FDF: ~100% vs 11% in 3 min; nitrendipine N-ODF: complete release in 3.5 min vs 30 min for tablet [81]).
 - Marked bioavailability gains (paroxetine OFDF ~178% relative to tablet; nitrendipine N-ODF significantly higher AUC in rabbits [24]).
 - Faster and greater mucosal permeation (repaglinide, paroxetine films 3-fold+ higher permeation vs pure drug [33,81]).

2. Vesicular and Lipid Nanocarriers in Films

- Niosomes with nisin were prepared by microfluidics and embedded into fast-disintegrating films, improving peptide stability and providing sustained release with preserved antimicrobial activity.
- Reviews highlight polymeric and lipid nanoparticles in ODFs for enhanced solubility, permeability, controlled release, taste masking, and stability [23,32].

3. Electrospun Nanofiber-Based FDFs

- Electrospun chitosan/pullulan or Na-caseinate/PVA nanofibers encapsulate aspirin or α -tocopherol acetate, dissolving

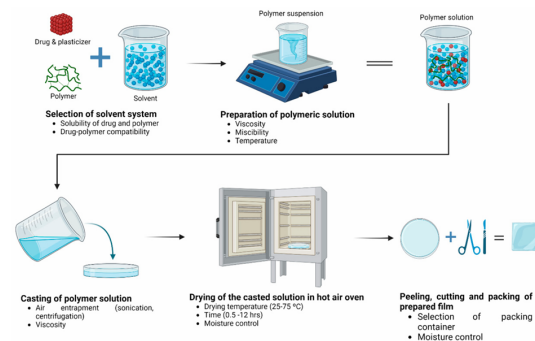
within seconds and improving release of hydrophobic bioactive [82,83].

- Cyclodextrin-based nanofibrous films (isoniazid/HP β CD) give nearly 100% loading, amorphous drug state, and disintegration in ~2 s with enhanced release promising for pediatrics [40,84].

Preparation Methods of fast dissolving films

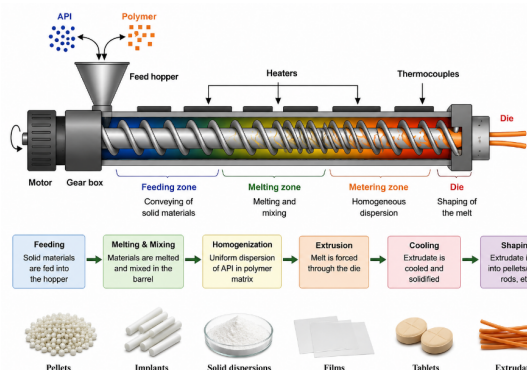
- **Solvent Casting**

The solvent casting method is the most popular method for formulation of phytoconstituents into polymeric dosage forms, such as oral films, buccal films and transdermal patches since it is a simple, economical and reproducible method which maintains the bioactivity of plant derived compounds [22,23,85]. The thermolability of many phytoconstituents like flavonoids, polyphenols, terpenoids, and alkaloids makes them vulnerable to degradation at high temperatures [49]. As the solvent casting process is typically conducted in ambient temperature or in mild drying conditions, it generally does not induce thermal degradation and helps ensure stability and pharmacological activity of these bioactive substances. In addition, solvent casting allows a uniform dispersion or dissolution of phytoconstituents in the polymeric matrix, resulting in uniform drug distribution and dose uniformity throughout the film. This technique also enables the addition of different functional excipients such as plasticisers, permeation enhancers, taste masking materials, antioxidants and stabilizers to achieve better physic-chemical characteristics and patient acceptability of the formulation. Moreover, it can be compatible with many natural and synthetic polymers including hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), sodium alginate, pullulan, pectin, and chitosan, which is very useful for herbal drug delivery [69,70]. Another advantage is that solvent cast films offer fast hydration, flexibility, and smooth surface morphology and have controlled drug release, which could enhance the bioavailability of poorly soluble phytoconstituents. In addition to the above, when the advanced delivery systems like phytosomes, nanoparticles or nanoemulsions are used in conjunction with solvent casting process, there will be an enhancement in the stability, intestinal absorption and therapeutic effects of the phytoconstituents. The solvent casting technique, due to these benefits, is one of the most widely adopted approaches for the production of phytochemicals containing polymeric films with pharmaceutical and nutraceutical applications [86].



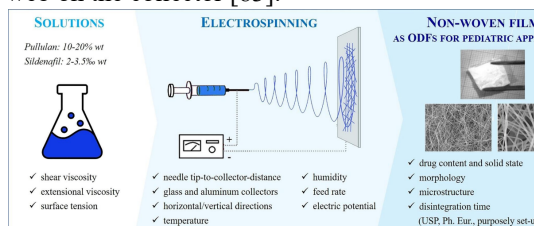
- **Hot Melt Extrusion**

Hot-melt extrusion (HME) is a pharmaceutical manufacturing method that is free of solvent, in which an active pharmaceutical ingredient (API) is mixed with one or more thermoplastic polymers and extruded under precisely controlled shear, pressure and temperature to form a homogenous solid dispersion or dosage form. In this process, the drug is dispersed uniformly or is molecularly dissolved in the polymer to be conveyed through a heated barrel and rotated by screws. The molten mass is then extruded through the die, chilled and formed into the desired dosage form, such as granules, pellets, film, implants or tablets [87,88]. HME has attracted significant interest in the pharmaceutical and nutraceutical fields due to its ability to improve the solubility, dissolution rate and bioavailability of poorly water-soluble molecules by turning crystalline drugs to amorphous solid dispersions [89]. The process is also environmentally friendly and cost-effective because it is entirely organic solvent-free, scalable and has a very high uniformity of content [90]. The use of HME for phytoconstituents, however, is restricted as many bioactive compounds found in plants are thermolabile and break down when exposed to high processing temperatures (usually 60-200°C, depending on the polymer used [88,89]). Hence HME can be used only with thermally stable phytoconstituents and/or with the use of low melting polymers and optimized processing conditions. In the case of heat sensitive phytochemicals, other methods like solvent casting, spray drying, freeze drying or incorporating into nanoparticles are generally preferred [91].



• Electrospinning

Electrospinning is a newly developed and versatile nanotechnology method for producing nanofibrous drug delivery system. It involves spinning the polymer solutions or polymer melts using high-voltage electric fields into ultra-fine fibers. The high surface-area-to-volume ratio, large porosity, interconnected pores and high surface area of electrospun nanofibers make them very promising drug delivery carriers [82,83]. The properties are useful for the formulation of fast dissolving oral films (FDOFs). The electrospinning technique is relatively simple. A polymer solution is put into a syringe with a metallic tip (a spinneret). The spinneret is connected to a high voltage and the collector is grounded. At a certain electric field strength, the surface tension of the polymer solution is overcome and the creation of Taylor cones starts at the spinneret. At the critical voltage, the jet of polymer solution is emitted from the cone and travels towards the collector. In flight, the solvent evaporates and the polymer forms a fine thread which is deposited as a fibrous web on the collector [83].



Nano fibres can be produced by electrospinning and used in the production of the FDOFs. The nanofibers have a large surface area which increases the surface area for saliva, and the film can be quickly dissolved. Then, the drug is released from the nanofibers into the oral cavity and absorbed through the oral mucosa. The route of administration is ideal for many drugs since

it bypasses the first pass metabolism in the liver [73]. The FDOFs may also enhance the pharmacological activity of the drug administered, improve its bioavailability, and decrease its gastrointestinal irritation. Easy to administer dosage form, especially beneficial for children, elderly and patients with swallowing problems.

There are two general types of electrospinning: solution electrospinning and melt electrospinning. The former is the most prevalent, and is applied to the production of nanofibers for pharmaceuticals. The method is a solution of drug and polymer in a volatile solvent or a mixture of solvents. As the jet of the polymer solution forms and moves towards the collector, the solvent is evaporated during this process. The method can be used to control the fiber diameter and can be used with temperature-sensitive biomolecules [83]. There is no need of solvents in melt electrospinning. The electric field melts the polymer and turns it into fibres at a temperature higher than its melting point. No toxic solvents are used and it is a safe process. It is difficult to employ the technique for molecules that are sensitive to heat, however, and requires temperatures higher than solution electrospinning.

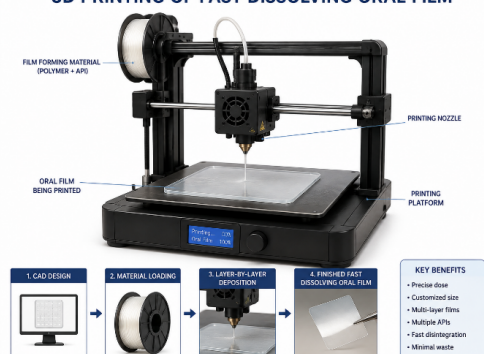
• 3D Printing

Three dimensional (3D) printing or additive manufacturing is a formative manufacturing process which creates three-dimensional objects through the successive deposition of materials under computer aided design (CAD). Three-dimensional (3D) printing is considered one of the innovative technologies with a great potential for manufacturing dosage forms with the intended dose shape, geometrical shape, function and property [92,93]. It allows high flexibility in terms of design and production and also provides unique opportunities to make more patient specific pharmaceutical products than it is possible by conventional techniques like solvent casting or hot melt extrusion [94,95].

The alternative dosage form to the traditional swallow tablets and capsules is fast dissolving oral films (FDOFs). The 3D printing technology could be utilized in order to manufacture films with the required properties including desired size, shape, thickness and drug contents with a specific release rate. Further, the 3D-printing process might result in manufacturing of oral film(s)

with a single or multiple active pharmaceutical ingredients (APIs), each having varying API release rate from the film. Such a method is more advantageous compared to the conventional solvent casting process due to multiple advantages including flexibility in terms of drug content and dosage forms, faster manufacture of the dosage forms with the intended patient-specific features and reduced amount of waste material since the printing process is precise and computer assisted [96,97]. It is critical to manufacture patient-tailored oral dosage forms with the capability to control the rate and extent of drug release for the management of various disease conditions including for children, elderly and people with swallowing problems [95].

3D PRINTING OF FAST DISSOLVING ORAL FILM



5. Critical Quality Attributes and Evaluation

Critical Quality Attributes (CQAs) are the physical, chemical, biological or microbiological characteristics or properties of the pharmaceutical product that must remain within their defined limits, ranges or distributions to ensure that the product quality, safety, efficacy and performance are as desired. Building quality into a product is an integral part of the Quality by Design (QbD) concept, as described in the International Council for Harmonisation (ICH) guideline Q8(R2) [98,99], the essence of which is to develop a product with quality in mind, rather than testing for it at the end of the process. Identification and control of CQAs are important in the case of fast dissolving oral films (FDOFs) which are designed to disintegrate rapidly in the oral cavity, and ensure delivery of the correct dose of the drug, prompt action and enhanced compliance by the patient. Changes in the critical quality attributes could have a profound impact on how the film performs mechanically, as well as on its disintegration, drug release profile, content uniformity, stability and therapeutic efficacy. Thus, optimisation of these CQAs is required to ensure a consistent quality of the product and reproducible manufacturing [100]. Selection of the appropriate

CQAs depend on the Quality Target Product Profile (QTPP) and scientific knowledge of the formulation and manufacturing process [101]. Both Critical Material Attributes (CMAs) including the type of polymer and its concentration, plasticizers, active pharmaceutical ingredients and other excipients and Critical Process Parameters (CPPs) such as mixing conditions, casting speed, drying temperature, drying time and manufacturing environmental conditions affect the CQAs. The understanding of the relationship between CMAs, CPPs and CQAs allow the formulation of a robust formulation that possesses predictable quality and performance. Appearance, film thickness, weight variation, drug content, content uniformity, surface pH, tensile strength, percentage elongation, folding endurance, Young's modulus, moisture content, moisture uptake, transparency, swelling behavior, disintegration time, dissolution profile, in vivo drug release and stability are the commonly evaluated CQAs for fast dissolving oral film [23,67,70]. These properties altogether affect the pharmaceutical quality, mechanical strength, satisfaction of the dosage form by the patient and its therapeutic efficacy. Therefore, Critical Quality Attributes identification, evaluation and optimization is a vital factor for the successful development of fast dissolving oral films, which ensures the consistency of the manufacturing process, compliance with regulatory requirements and a consistent therapeutic effect during the product's shelf life.

A) . Physicochemical Characterization

Thickness, weight, content & surface properties

- FDFs are routinely checked for thickness, weight variation, drug content, surface pH, moisture content/uptake, and morphology (SEM/optical microscopy) to ensure dose accuracy and patient comfort. Ensures dose accuracy and reproducibility. Uniform thickness (commonly 20–200 μm) and weight across the batch are essential for consistent drug content per film [23,100].
- Typical films show very low variability and ~98–100% drug content, with surface pH near salivary pH ($\approx 6-7$) to minimize irritation [31,76].

Mechanical Properties

- Along with tensile strength, % elongation and folding endurance, some studies also report Young's modulus as stiffness indicator; ideal films combine moderate strength, high elongation, low modulus, and high folding endurance (>100–300) for handling and mouth movements [78].
- Automatic folding endurance rigs have been proposed to standardize this test and show

that FE reflects both strength and extensibility, not just “brittleness”.

B). Disintegration and Dissolution

- FDFs usually aim for disintegration times of a few tens of seconds; many optimized films report 7–40 sec [70,102].
- Dissolution is often evaluated with USP II paddle, using small volumes or simulated saliva; >80–100% release within 2–15 min is common for successful formulations [103,104].
- For strip films containing nano- or microparticles, both USP I and USP IV have been explored; USP IV showed better discrimination between nano- and micro-particle release and is suggested as a powerful tool for such systems [103].
- A recent review summarizes apparatus choices, media (including simulated saliva), volumes and method development for films, and highlights their role in IVIVC and quality control [91,103]

C). Mucoadhesion

- The term “mucoadhesion,” sometimes known as “bioadhesion,” describes how a pharmacological dosage form or delivery mechanism adheres to the mucosal epithelium [105,106]. Increasing the dosage form's contact time with the mucosal membrane might improve drug absorption for many medications meant to be supplied by transmucosal methods. Increasing the strip's residence time in the mouth or gastrointestinal system may assist improve the bioavailability and absorption rate of many APIs, including thin-film formulations [72].
- For buccal films, mucoadhesive strength, residence time and swelling/hydration are central; films are often tested on porcine buccal tissue or model gels using texture analyzers to measure detachment force and work of adhesion [85,107].
- Reported mucoadhesive strengths in optimized buccal films are typically sufficient to ensure several hours' residence without causing damage, while maintaining acceptable mechanical flexibility [85,107].
- Reviews catalogue many setups (tensiometric, shear, rheological) and stress the lack of compendial standards, recommending method selection based on intended site and residence time [106,108].

D). In Vivo & Permeation Studies

- **Ex vivo permeation:** Franz diffusion cells or flow-through setups with porcine/bovine buccal mucosa are widely used to determine flux, lag time and permeability coefficients; hydration and mucoadhesion are often measured in parallel [108,109].
- **Pharmacokinetics:** Multiple buccal and fast films show higher C_{max} and AUC and/or shorter T_{max} versus oral solutions or tablets, with relative bioavailability up to ~2–2.5 fold in rabbits for rizatriptan and tizanidine/meloxicam films [33,110].
- For FDFs intended mainly for rapid GI absorption, PK studies in animals or humans compare FDFs to conventional oral forms to demonstrate faster onset and sometimes improved exposure [23,67].

6. Case Studies: Successful Phytoconstituent-Loaded FDFs

The rising popularity of herbal drugs and medicinal plants and their bioactive compounds, novel drug delivery systems have been developed to address the challenges faced in traditional herbal medicine formulations [13,14]. The phytoconstituents such as polyphenols, flavonoids, alkaloids, terpenoids, glycosides and other naturally occurring compounds have broad Pharmacological properties like antioxidant, anti-inflammatory, antimicrobial, anticancer, antidiabetic, neuroprotective, cardioprotective and immunomodulatory. Many phytoconstituents, however, due to their therapeutic potential, suffer from poor aqueous solubility, poor permeability, chemical instability, rapid metabolism and high first-pass hepatic metabolism, causing them to have low bioavailability in the oral route of administration and inconsistent therapeutic response [12,15]. This has stimulated researchers to research advanced drug delivery methods that can enhance the pharmaceutical and biopharmaceutical characteristics of herbal bioactive compounds [17]. Fast dissolving oral films (FDFs) are emerging as a novel and convenient drug delivery system for delivering phytoconstituents which are patient friendly. These thin polymeric films hydrate and disintegrate quickly on the tongue and/or the buccal mucosa, resulting in the release of active compounds within a short time without the need for water. They have a large surface area and are very thin - their close contact with the oral mucosa ensures rapid dissolution and in the case of appropriate compounds, uptake by the oral mucosa or sublingual membrane. This can decrease first pass metabolism, increase bioavailability, and increase the rapidity of onset of therapeutic effect and treatment success [33,66]. FDFs are also highly patient convenient and are especially useful for patients with swallowing difficulties such as those with dysphagia,

bedridden patients, geriatric and pediatric patients [25,26]. The fast-dissolving oral film has been further developed in recent years, and there are many new formulations available for herbal drug delivery. The use of phytoconstituents as nanocarriers such as phytosomes, nanoparticles, nanoemulsions, liposomes, polymeric micellar, solid dispersion and cyclodextrin inclusion complex, prior to the formation of film, has highly enhanced the solubility, dissolution rate, stability, permeability and oral bioavailability of many poorly soluble herbal compounds [21,40,52]. Appropriate film-forming polymers, plasticizers, saliva stimulating agents, sweeteners, flavouring agents and manufacturing methods, such as solvent casting, hot-melt extrusion, electrospinning, and 3D printing, have allowed the creation of an oral film with an excellent mechanical property, fast disintegration, high drug loading efficiency and reproducible drug release profile [82,86,87,92]. A number of studies have been successful with the use of phytoconstituent loaded fast dissolving oral films that have shown improved therapeutic effect and patient compliance. Various herbal compounds like *curcumin*, *quercetin*, *resveratrol*, *berberine*, *catechins*, *ginger extract*, *Bacopa Monnieri*, *Withania somnifera* (Ashwagandha), *Centella asiatica* and other bioactive agents of plant origin have been successfully included in oral film formulations [111–114]. The results of these studies have been consistently reported to be better dissolution rate, drug release, bioavailability, mechanical strength, stability, and acceptability of the drug to the patient than with conventional dosage forms [23,24].

Moreover, some of the formulations proved to have increased pharmacological activity thanks to improved delivery of the phytoconstituents. Some exemplar case studies of phytoconstituent loaded fast dissolving oral films reported in the literature are presented below. The investigations have demonstrated the impact of formulation strategies, type of polymer used, preparation method, and assessment methods on the efficacy of herbal oral films. The results of these studies indicated that the fast-dissolving oral film technology is a promising approach to deliver phytoconstituents, and could be adapted to its use in personalized, patient-centric, herbal drug delivery systems [32,95].

Curcumin-Loaded Fast Dissolving Films

The main polyphenolic compound of *Curcuma longa* (turmeric) has strong antioxidant, anti-inflammatory, antimicrobial, anticancer, and wound healing effects [37,38]. However, its therapeutic application is restricted due to its low aqueous solubility, low permeability, rapid metabolism and low oral bioavailability. To resolve these restrictions, fast dissolving oral films (FDOFs) have been studied as an alternative to drug delivery system. The curcumin

loaded FDOF are engineered to disintegrate rapidly in the oral cavity, thus allowing the fast release of the drug, better dissolution and absorption. Hydrophilic polymers, hydroxypropyl methylcellulose (HPMC), pullulan, polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP) are widely used as film forming agents, and plasticizers such as glycerol and polyethylene glycol (PEG) increase the flexibility and mechanical properties of the films [70,77]. Oral films have also been developed using advanced formulation techniques such as using nanoparticles, phytosomes, nanoemulsions, and solid dispersions for further enhancement of the solubility and bioavailability of curcumin [37,42]. It has been shown that curcumin containing oral films have uniform drug content, good mechanical properties, rapid disintegration, better dissolution and greater bioavailability than conventional oral dosage forms. These films have been shown to have a potential for local oral therapy and systemic drug delivery and are patient friendly dosage forms especially in paediatric, geriatric patients and dysphagic patients [25,111].

Several studies have developed curcumin-loaded FDFs with promising results [111]:

- A study developed curcumin-loaded FDFs using HPMC and pullulan as film formers, with incorporation of curcumin in a self-emulsifying system to enhance solubility. The formulation showed rapid disintegration (28 seconds) and significantly enhanced in vitro permeation across buccal mucosa compared to curcumin suspension.
- Another approach incorporated curcumin-loaded Nanosponges into HPMC-based films, achieving a 4.5-fold increase in dissolution rate and enhanced anti-inflammatory activity in animal models.

Quercetin Fast Dissolving Films

Quercetin is a naturally occurring flavonol, which is present in fruits and vegetables as well as in tea and medicinal plants. It has diverse pharmacologic properties such as antioxidant, anti-inflammatory, antiviral, antimicrobial, anticancer and cardioprotective properties [115,116]. The therapeutic potential of quercetin is extensive, but the use of this compound in clinical applications is restricted due to its low aqueous solubility, low oral bioavailability and significant first-pass metabolism [53,117]. A new drug delivery system that looks promising for overcoming these limitations are fast dissolving oral films (FDOFs). The drug release rate from the quercetin loaded FDOFs is faster and the drug dissolves better in the oral cavity because the FDOFs disintegrate quickly. Hydrophilic polymers like hydroxypropyl

methylcellulose (HPMC), pullulan, polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP) are commonly used for film preparation, and plasticizers like glycerol and polyethylene glycol (PEG) improve film flexibility and mechanical strength. Oral films containing advanced formulation techniques such as nanoparticles, solid dispersions and cyclodextrin inclusion complexes have also been used to enhance the solubility and bioavailability of quercetin [40,42]. It has been shown that quercetin contained in fast dissolving oral films have uniform drug content, good mechanical properties, rapid disintegration, enhanced drug dissolution and improved bioavailability to the conventional oral delivery systems. A potential patient-friendly drug delivery system, they demonstrate increasing therapeutic efficacy and compliance with the patient, especially in children, elderly and dysphagic patients.

Quercetin-loaded FDFs developed using sodium alginate and HPMC demonstrated:

- Complete disintegration within 45 seconds
- Enhanced dissolution (95% release within 10 minutes compared to 20% for pure quercetin)
- Improved antioxidant activity as measured by DPPH radical scavenging assay

Silymarin Fast Dissolving Films

Silymarin is a flavonolignan complex isolated from the seeds of *Silybum marianum* (milk thistle) and is well-known for its hepatoprotective, antioxidant, anti-inflammatory, antifibrotic and anticancer effects [118,119]. It is a common agent used in the management of various liver conditions such as drug induced liver injury, cirrhosis and hepatitis. The therapeutic activity of Silymarin is however restricted by its low gastrointestinal absorption, aqueous insolubility and low oral bioavailability [52,120]. An effective drug delivery system to improve the pharmaceutical performance of silymarin are fast dissolving oral films (FDOFs). These films quickly dissolve in the mouth, allowing the medication to dissolve quickly and absorb better into the body. Film preparation is often carried out with the use of hydrophilic polymers like hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), pullulan and polyvinylpyrrolidone (PVP), and plasticizers like polyethylene glycol (PEG) and glycerol to provide flexibility and mechanical strength. Moreover, formulation approaches, such as solid dispersion, nanoparticles and phytosomes have been investigated to improve the solubility and bioavailability of silymarin [52,120]. The silymarin containing fast dissolving oral films have been reported to possess good mechanical strength, satisfactory uniformity of drug content, disintegration, dissolution and bioavailability characteristics when compared with the conventional oral dosage forms. As

such, the use of silymarin loaded FDOFs could be a promising patient friendly dosage form that may enhance the therapeutic effect and patient compliance, especially in those who have trouble swallowing in the regular tablet or capsule.

Silymarin-loaded FDFs prepared using PVA and HPMC showed:

- 85% drug release within 15 minutes
- Enhanced hepatoprotective activity in CCl₄-induced liver damage models
- Improved patient compliance compared to conventional tablets

Green Tea Extract (EGCG) Films

Green tea extract, extracted from *Camellia sinensis* leaves, contains high concentrations of the catechins, with epigallocatechin-3-gallate (EGCG) being the leading bioactive compound. EGCG has been shown to have strong antioxidant, anti-inflammatory, antimicrobial, anticancer, and cardioprotective properties [121,122]. Although EGCG has therapeutic potential it is poorly bioavailable in the oral cavity because of its poor stability, oxidation and rapid metabolism [50,123]. A new dosage form, called fast dissolving oral films (FDOFs), has been developed as an effective delivery system to stabilize and improve the bioavailability of EGCG. Such films dissolve very quickly in the mouth and provide rapid release of the drug, which aids in its dissolution. The most important film-forming agents are the hydrophilic polymers, such as hydroxypropyl methylcellulose (HPMC), pullulan, polyvinyl alcohol (PVA), and sodium alginate, whereas the most important plasticizers are glycerol and polyethylene glycol (PEG), which improve flexibility and mechanical properties. Various approaches to the protection of EGCG from degradation and increased therapeutic effect have also been investigated, such as encapsulation using nanoparticles and liposomes [17]. It has been shown that EGCG loaded fast dissolving oral films have uniform drug distribution, good mechanical properties, fast disintegration and enhanced dissolution. These films have demonstrated its potential in the treatment of oral infections, periodontitis, oral ulcers, and systemic diseases that need antioxidant therapy [122]. Thus, EGCG incorporated fast dissolving oral films are a promising patient friendly dosage form that enhances stability, bioavailability and therapeutic efficacy.

EGCG-loaded chitosan-based FDFs demonstrated:

- Enhanced stability of EGCG over 6 months
- Rapid buccal absorption with 2.5-fold higher bioavailability compared to oral solution
- Effective antioxidant activity maintained

Berberine Fast Dissolving Films

Berberine is a naturally occurring isoquinoline alkaloid isolated from medicinal plants such as *Berberis aristata*, *Berberis vulgaris*, and *Coptis chinensis*. It possesses a wide range of pharmacological activities, including antidiabetic, antimicrobial, anti-inflammatory, antioxidant, antihyperlipidemic, and cardioprotective effects [124,125]. However, its clinical application is limited by poor aqueous solubility, low intestinal absorption, extensive first-pass metabolism, and consequently low oral bioavailability [126,127].

Fast dissolving oral films (FDOFs) have been investigated as an effective drug delivery system to improve the pharmaceutical performance of berberine. These films rapidly disintegrate in the oral cavity, facilitating faster drug release and enhancing dissolution and absorption. Film-forming polymers such as hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), pullulan, and polyvinylpyrrolidone (PVP) are commonly employed, while plasticizers such as glycerol and polyethylene glycol (PEG) improve film flexibility and mechanical strength. Advanced formulation approaches, including nanoparticles, solid dispersions, and liposomal systems, have also been explored to enhance the solubility and bioavailability of berberine [126].

Studies have demonstrated that berberine-loaded fast dissolving oral films exhibit uniform drug content, satisfactory mechanical properties, rapid disintegration, enhanced dissolution, and improved bioavailability compared with conventional oral dosage forms. Owing to these advantages, berberine-loaded FDOFs offer a promising patient-friendly dosage form for improving therapeutic efficacy and patient compliance, particularly in the management of metabolic disorders and microbial infections.

Berberine-loaded FDFs incorporating P-gp inhibitors (e.g., piperine) showed [127,128]:

- 3.2-fold increase in C_{max} compared to berberine tablets
- Improved oral glucose tolerance in diabetic animal models
- Enhanced permeability across buccal mucosa

7. Regulatory Considerations

Fast dissolving oral films (FDOFs) are an innovative oral drug delivery system, which are expected to disintegrate quickly in the mouth, be easy to swallow and are expected to enhance patient compliance especially in children, geriatric patients and dysphagic patients. This dosage form is increasingly being adopted in the commercial and clinical setting, and regulatory bodies have developed a set of quality and manufacturing requirements to assure that FDOFs are safe, effective, and of good quality. There is no international guideline that is specific to fast

dissolving oral films, but the development is governed by general pharmaceutical guidelines for dosage forms in the oral route, quality systems and pharmaceutical manufacturing [129]. Important regulatory agencies such as the United States Food and Drug Administration (USFDA), the European Medicines Agency (EMA), the Central Drugs Standard Control Organization (CDSCO, India), the Medicines and Healthcare products Regulatory Agency (MHRA, UK), the Pharmaceuticals and Medical Devices Agency (PMDA, Japan), and the Therapeutic Goods Administration (TGA, Australia) impose the major regulatory requirements for FDOFs [129]. These agencies must convince manufacturers that the oral films have uniform drug content, predictable drug release, acceptable mechanical properties, uniform quality, and rapid disintegration and stability during the shelf life. Pharmaceutical development for FDOFs is based on guidelines set by the International Council for Harmonisation (ICH) which provide globally harmonized guidelines. The ICH Q8(R2) guideline encourages the use of Quality by Design (QbD) in which the manufacturers define the Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs), and establish the design space for consistent product quality [98,101]. ICH Q9 is dedicated to Quality Risk Management, and this will help manufacturers identify and manage risks related to formulation variables, manufacturing processes and product performance [130]. ICH Q10 is the Pharmaceutical Quality System that can facilitate the process of continual improvement throughout the product lifecycle [131], and ICH Q2(R2) is a recommendation for analytical method validation [132]. ICH Q1A(R2) provides guidelines for stability testing under long-term, intermediate and accelerated storage conditions [133]. Current Good Manufacturing Practices (cGMP) are standards imposed by regulatory agencies for the conduct of all manufacturing activities.

Important operations like solution preparation, mixing, casting, drying, cutting, packaging and storage must be validated by manufacturer. Production facilities need to be under controlled environment conditions, equipped with qualified equipment, staffed with trained personnel, and have full documentation to ensure that each production batch is the same and reproducible. Quality control is an important regulatory criterion for fast dissolving oral films. All finished products should be tested for appearance, thickness variation, drug content, content uniformity, tensile strength, folding endurance, percentage elongation, surface pH, moisture content, moisture uptake, disintegration time, dissolution profile, in vitro drug release, microbial limits and stability. Assessment techniques for these evaluations should be

scientifically validated for reliability, accuracy, precision and reproducibility. Packaging is also a key element in product regulations oral films are very sensitive to moisture, oxygen and light. To ensure the integrity of the product during storage and handling, it is recommended to use the protective packaging material like aluminium foil sachets, laminated pouches or blister packs [24]. Packaging systems also need to be tested to ensure that they are able to protect the product under recommended storage conditions. Regulatory expectations are even greater for a phytoconstituent- or herbal-loaded fast dissolving oral film than for a synthetic drug. Manufacturers have to prove that their extracts are botanically authenticated, extracted according to the standards established by the botanical route, marker compound(s) identified and quantified, and that their products are consistent from batch to batch and meet limits for microbial contamination, heavy metals, pesticide residues, aflatoxins, and residual solvents [134–136]. The extra requirements are required as natural products can present higher level of variation than synthetic active pharmaceutical ingredients [137,138].

Typically, regulatory submissions for fast dissolving oral films are done in the Common Technical Document (CTD) or electronic Common Technical Document (eCTD) format. The submission contains complete details on product development, pharmaceutical formulation, manufacturing process, analytical method validation, process validation, stability studies, specifications, packaging and clinical or bio-equivalence data (where applicable). The data on these are evaluated by regulatory authorities to decide if the product consistently meets specified quality, safety, and effectiveness requirements. Once the market is approved, the manufacturer must keep compliance by continuous pharmacovigilance [139], periodic quality reviews, change control, deviation management, complaint handling, and monitoring stability. Verifying the continuous process and lifecycle management ensures that the product is safe and effective during its entire commercial life. Finally, the regulatory framework of fast dissolving oral films is not a dosage form-specific regime, but is based on internationally harmonized pharmaceutical quality standards. Successful development, regulatory approval and commercialization of FDOFs relies on compliance with ICH guidelines, cGMP requirements, Pharmacopeial standards and on robust quality management systems to ensure quality and safety. With increasing interest in personalized medicine and the development of new oral drug delivery systems, additional regulatory guidance for oral films is anticipated that will foster innovation and uphold product quality and patient safety [129].

8. Challenges and Future Perspectives

8.1. Current Challenges

- **Low Drug Loading Capacity**

A key drawback of fast dissolving oral films (FDFs) is that the amount of phytoconstituent or active pharmaceutical ingredient (API) which can be incorporated into each film is inherently limited due to the thin and lightweight film [22,31]. This is generally acceptable for the very potent phytoconstituents, which are therapeutic at low doses. Many herbal extracts, however, need a relatively high amount of dose to reach the desired pharmacological effect which is the challenge in incorporating into FDFs. The drug loading could impact the thickness, flexibility, mechanical strength, uniformity, and disintegration time of the film, which could ultimately impact the quality of the product and patient acceptance. Hence, the use of FDFs is limited to low doses of phytoconstituents unless sophisticated formulation techniques like nanoparticles, solid dispersions, phytosomes and nanocarriers systems are used to increase the loading of the active ingredients and therapeutic efficacy [23,81].

- **Stability of Phytoconstituents**

One of the main difficulties in the formulation of fast dissolving oral films (FDFs) is their stability of the phytoconstituents. The environmental factors affecting many plant-derived bioactive compounds include light, heat, oxygen, moisture, and pH, which can cause degradation, loss of efficacy and shorter shelf life [49–51]. Also, hydrophilic polymers which are commonly used in FDFs can absorb moisture and induce the degradation of moisture sensitive phytoconstituents and change the mechanical characteristics of the film [23]. Encapsulation (e.g., phytosomes, nanoparticles or liposomes), antioxidants, inclusion of appropriate excipients and moisture protection of the package are some of the formulation options used to enhance stability. In addition, stability study as per ICH guidelines is necessary to guarantee the quality, safety and therapeutic efficiency of the phytoconstituent-containing fast dissolving oral films during their life span [133].

- **Standardization of Herbal Extracts**

A standardization of herbal extracts is one of the most important problems to be solved in the development of fast dissolving oral films (FDFs). Herbal extracts are composed of

several bioactive compounds that can change depending on the plant species, geographical origin, cultivation conditions, harvest time, and extraction process [137,138], as opposed to synthetic drugs. This variability may result in inconsistent drug content, efficacy and quality product. Thus, it is important to standardize herbal extracts with identification and quantification of marker compounds and batch-to-batch consistency. Standardization enhances the safety, efficacy, stability, and repeatability of phytoconstituent containing fast dissolving oral films, as well as their regulatory acceptance [136,139].

• Regulatory Hurdles

The regulatory pathway for botanical drug products is more complex than for synthetic drugs, with requirements for demonstrating consistent composition and biological activity [134,137].

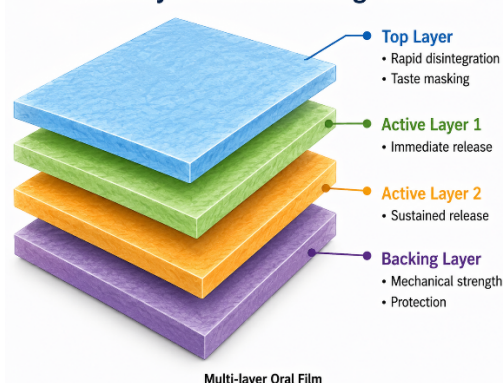
8.2. Future Perspectives

Multi-Layer Films

The multi-layer films are an innovative development in fast dissolving oral film (FDOF) technology in which two or more layers are integrated into a single dosage form; each layer has a different therapeutic function. These films allow for loading one or more active pharmaceutical ingredients (API) with various release profiles, including immediate, sustained or sequential drug release. This technology can be especially useful to provide a combination therapy, whereby two or more drugs can be delivered simultaneously in the formulation while avoiding possible drug–drug interactions [140].

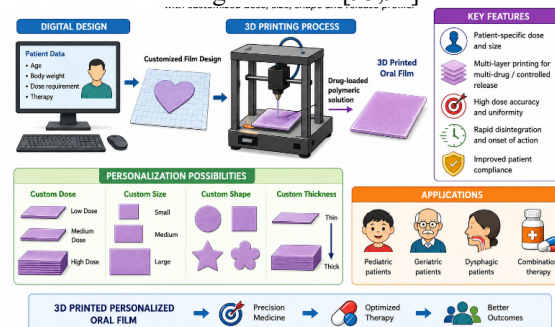
For oral films containing phytoconstituents, the multi-layer design can provide better stability of the sensitive phytoconstituents by dividing incompatible active ingredients into each layer. They offer the flexibility of incorporating synthetic drugs with phytoconstituents, which can improve therapeutic outcomes and patient convenience. With the recent development of solvent casting, hot-melt extrusion and 3D printing, oral films with precisely controlled thickness, drug loading and release properties are now achievable, allowing for the development of multi-layer films. Thus, multi-layer FDOFs have great potential applications in personalized medicine and next generation oral delivery of the drugs [97,140].

Multi-Layer Fast Dissolving Oral Film



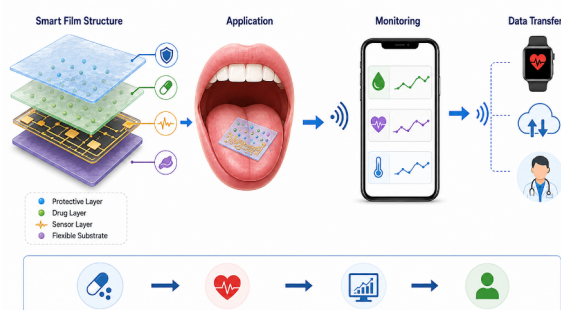
Personalized Films via 3D Printing

Three-dimensional (3D) printing is a technology that appears to be a promising method for manufacturing personalized fast dissolving oral films (FDOFs). In contrast to traditional manufacturing processes, 3D printing allows the creation of patient-specific oral films that can achieve customised drug dosage, size, shape, thickness and release profile according to the therapeutic requirements of each patient [92,96]. This technology enables the precise layer-by-layer deposition of drug-containing material with high dose accuracy and even distribution of the drug. Personalized 3D printed oral films are especially valuable for children, elderly, and dysphagic patients as they may need individual dose and convenient dosage forms. Moreover, 3D printing allows for inclusion of several active pharmaceutical ingredients (APIs) within a single film, which can be either delivered immediately or be released gradually or sequentially, thus enabling combination therapy and adherence to treatment. The development of precision medicine oral films is expected to be further speeded by the recent progress in 3D printing, Quality by Design (QbD) and digital healthcare technologies. However, while there are still obstacles to be overcome such as large-scale manufacturing issues, regulatory clearance, and material selection, there is potential that 3D printing can revolutionise the future of the fast-dissolving oral films [93,94].



Smart Films with Sensors

Smart films incorporating biosensors is a novel example of fast dissolving oral film (FDOF). These are advanced films that can track physiological parameters or therapeutic response in real-time, and also deliver the drug. The embedded biosensors can measure the release of drugs and the efficacy of the therapy in real time, allowing for monitoring of drug effects or the presence of biomarkers, such as pH, glucose, enzymes, or other specific markers [141,142]. The collected data can then be fed into digital healthcare systems or wearable devices, aiding personalized treatment and prompt clinical decision-making. While in the research phase, sensor-integrated smart films can hold great promise in medicine adherence, drug optimization and precision medicine, making them a promising future ahead in oral drug delivery [141].



Combination with Other Bioavailability Enhancers

A novel formulation technology of combining fast dissolving oral films (FDOFs) with bioavailability enhancers is a promising approach for enhancing the absorption and therapeutic actions of poorly soluble drugs and phytoconstituents. The use of formulation techniques like nanoparticles, phytosomes, liposomes, nano emulsions, solid dispersions, polymeric micelles and cyclodextrin inclusion complexes improve the solubility, stability, permeability and bioavailability of the drug [21,40]. Also, permeation enhancers and mucoadhesive polymers aid in the absorption of the drug into the oral mucosa [33,34]. Such an approach would be especially useful for phytoconstituents like curcumin, quercetin, silymarin, berberine and EGCG, and could broaden the scope of FDOFs to achieve optimal and patient-friendly drug delivery [17].

Application for Large Molecules

The delivery of large molecule drugs, such as peptides, proteins, vaccines and nucleic acid-based drugs, using the application of Fast dissolving oral films (FDOFs) is a growing area of pharmaceuticals research. These biomolecules tend to have very low bioavailability in the oral cavity because of enzymatic degradation and inability to absorb in the gastrointestinal tract [143]. FDOFs can be administered via buccal or sublingual administration, thereby avoiding the first pass metabolism [34,143]. Additionally, permeation enhancers, nanoparticles and mucoadhesive polymers

are incorporated to improve the delivery of large molecules. While stability and permeability issues still need to be addressed, FDOFs offer great potential for the delivery of biologics and other advanced therapeutics without the need of invasive procedures.

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