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Oral Fast Disintegrating Films of Phytochemicals: A Novel Drug Delivery System

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Abstract

Oral fast disintegrating films (OFDFs) have been developed as a viable alternative to conventional oral solid dosage forms such as tablets, capsules, and syrups for patients who struggle consuming them. OFDFs are thin strips that disintegrate or dissolve rapidly when placed in the oral cavity, allowing quick onset of action. These films are prepared by incorporating active pharmaceutical ingredients with film-forming polymers and other ingredients. OFDFs are also developed by incorporating active constituents present in phytochemicals such as flavonoids and polyphenols. In recent years, researchers have developed OFDFs by incorporating active phytoconstituents and/or herbal extracts to produce significant therapeutic activity. Phytochemical-based OFDFs show pharmacological activities such as anti-inflammatory, antiviral, immunomodulatory, antimigraine, antiarrhythmic, antioxidant and antibacterial. These films can also be used in the management of dementia, cerebral insufficiency and Alzheimer's disease. The present review focuses on the formulation and development of phytochemical-loaded OFDFs and recent research carried out on the same in tabular form.

Keywords: Oral fast disintegrating film, phytochemicals, active phytoconstituents, herbal extracts, natural active compounds, oral mucosa, mouth dissolving film

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Introduction

The oral route is widely used for the administration of therapeutic agents because of its simplicity of administration, non-invasiveness, flexibility, and patient acceptance, the oral route is the most favored mode of drug administration for systemic impact.[1, 2] Because of the convenience of manufacture, shipping, and patient acceptance, tablets are the most used dosage form. Patients who are geriatric, pediatrics, nauseated, or non-compliant have difficulty swallowing traditional oral dose forms. It is believed that half of the population is afflicted by this issue, which leads to a higher risk of non-compliance and inefficient treatment. To master this, oral fast disintegrating drug delivery systems were developed by scientists at Wyeth Laboratories in late 1970s in the United Kingdom as a replacement of tablets, capsules, and syrups for children and elderly people who have a tough time administering conventional solid dosage forms for oral administration. Mouth dissolving tablets and oral fast disintegrating films (OFDF) are two types of oral fast disintegrating dosage forms. Although their fast disintegration or dissolution times, there is still a dread of taking mouth dissolving tablets. Mouth dissolving tablets are related to some issues, including the presence of residue in the mouth, which produces a grittiness in the mouth and there is fear of choking and trouble administering tablets. To overcome the problems associated with mouth dissolving tablets, a novel drug delivery technology called oral fast disintegrating films (OFDF)/ oral dispersible films/ mouth dissolving films was developed.[2, 3] OFDF was created using the same technology as transdermal patches for oral medication administration. OFDFs are made of hydrophilic polymers that dissolve fast when applied on the tongue or in the buccal cavity, where the film absorbs saliva and hydrates quickly, allowing the medication to be absorbed orally. The rapid disintegrating action is mostly due to the surface area of the film wetting rapidly when exposed to the moist oral environment[2, 3]. OFDFs improve bioavailability, reduce therapeutic costs, and make administration easier, all of which patient compliance increases. Films are administered through the oral mucosal route to achieve a minimum disintegration time in the oral mucosa in order to reach systemic circulation with the quickest onset of action[4]. Over the last two years, consumers have been introduced to this approach through the release of several breath refreshing products. Today, OFDFs are already a proven and welcomed technique used for the systemic administration of APIs in OTC medications.[3]

Phytochemicals can be incorporated in the formulation and development of OFDFs to produce pharmacological activities. Recent studies show that phytochemicals produce a wide range of therapeutic effects and help in the management of certain disorders. Phytochemicals such as flavonoids, polyphenols, glycosides, saponins, etc. and active constituents present in them are employed in the formulation. Active phytoconstituents such as quercetin, herpetrione, curcumin, etc. can be formulated with film-forming polymers and other ingredients to obtain film. Certain herbal extracts of peanut, propolis, olive leaf, etc. can also be used as natural active compounds in the formulation and development of OFDFs for therapeutic roles. The extracts are obtained by several extraction techniques such as ethanol extraction, bleaching, decoction and maceration. These natural active compounds have anti-inflammatory, antiviral, immunomodulatory, antimigraine, antiarrhythmic, antioxidant and antibacterial activities. Phytochemical-based OFDFs can be used in the management of Alzheimer's disease, dementia and cerebral insufficiency. Researchers have developed many OFDFs using phytochemicals as an active ingredient.

Absorption pathway through oral mucosa:[4, 5]

For passive drug diffusion over the oral mucosa, there are two penetration pathways: route paracellular and transcellular. Permeants can use both pathways at the same time. However, according to the physicochemical features of the diffusing medication, one route is generally favored over the other. Owing to the lipophilic nature of the cell membrane, hydrophilic solutes will have difficulties passing through it because of the partition coefficient. As a result, the intercellular space is the primary barrier to lipophilic solute penetration, whereas the cell membrane is the primary barrier to hydrophilic compound transport. The penetration of the compound via the oral epithelium may employ a mixture of these methods. [4]

Perks of OFDFs:

- Effective in conditions requiring a quick initiation of effect, such as motion sickness, allergic reactions, sneezing, or asthma.
- OFDFs are more flexible than other conventional medicaments and therefore provide more patient compliance.[7]
- Oral film drug administration offers the potential to enable the production of sensitive drug targets that would otherwise be difficult to obtain in solid or liquid formulations.[8]
- From a business aspect, marketing innovative dosage form (OFDF) would help the business to gain more revenue.[3]

Limitations of OFDFs:

- Dose termination is impossible, as they disintegrate rapidly.
- The physiochemical properties of the drug must be desirable in order for it to permeate from the buccal mucosa.[9]
- Drugs that are reactive at buccal pH and drugs that irritate the mucosa are not suitable for this route of administration.[10]

Classification of OFDFs:[6]

OFDFs are categorized into three types.

1) Flash release
2) Mucoadhesive melt-away wafers
3) Mucoadhesive sustained released wafers

Formulation and Development of Phytochemical Loaded OFDFs:

Hydrophilic polymers and one or more active phytochemical constituents make up oral fast disintegrating films (OFDFs). Polymer science obtained from traditional solid transdermal and oral drug formulations is used in the development of OFDFs. Manufacturers can efficiently develop novel medicines within a shorter development period by using their similarities. Because of the versatility in the formulation of oral thin film technology, manufacturers can pick from a wide range of phytocompounds and excipients when developing new products. Material selection depends on film disintegration rates and absorption rates, such that a drug that is similar to or better than existing formulations such as pills, liquids, and capsules may be designed.[11] Several breath-freshening OFDFs have been released in the previous two years, introducing customers to this method.[3]

Formulation Aspect:

Mechanical characteristics, taste concealing, quick-dissolving, personal features, and tongue feel are all factors to consider while formulating.[12] OFDF is a thin film/strip incorporating an active constituent with a surface area of 1-20 cm2 (depending on dosage and drug loading). The active ingredient can be incorporated up to 30 mg in one dosage.[6] All ingredients included in the composition of thin film should be generally considered suitable and approved for use in oral pharmaceutical dosage forms, according to regulatory guidelines.[13] Table 1 displays the composition of OFDFs as well as the numerous chemicals employed in their production.

Table 1: Standard composition of OFDFs:[1, 3, 4]

Ingredients	Amount (%w/w)	Example
Drug	5-30	Antiallergic, Anti-inflammatory, Antimigrant, Antioxidant, Antiviral, etc.
Film-forming polymers	30-50	Gelatin, HPMC E3/E5/E15, CMC, Starch, etc.
Plasticizers	0-30	Glycerol, Sorbitol, Glycerin, PEG-400, Propylene glycol, etc.
Surfactants	q. s.	Sodium dodecyl sulfate, Sodium lauryl sulfate, Sorbitan oleate, Tween-80, etc.
Sweetening agents	3-6	Saccharin, Cyclamate, Aspartame, Sucralose, Alitame, Neotame, Sucrose, Dextrose, etc.
Superdisintegrants	5-8	Microcrystalline cellulose, Sodium starch glycolate, Polacrilin potassium, etc.
Saliva stimulating agents	2-6	Citric acid, Malic acid, Lactic acid
Thickening agents	5	Xanthan, Guar, Cellulosic derivatives
Colors	<1	FD and C colors
Flavors	5-10	US FDA approved flavors

1. Drug

A number of active phytochemicals can be integrated into the fast-dissolving oral thin film technique. The ideal components for the formulation of oral thin films are low dosage active phytoconstituents.

Characteristics of drugs to be included in OFDFs[2, 14]

- The therapeutic dosage of the drug should not exceed 30mg, and it should generally account for 5-30% w/w of the final dosage form.[12]

- The drug's solubility and stability in water/saliva and mouth should be excellent.

a) Table 2 lists suitable phytoconstituents and herbal extracts for inclusion into thin film formulations.

Table 2: Suitable phytoconstituents and herbal extracts for incorporation into thin film formulation

Active phytoconstituents	Herbal extracts
Herpetrione	Peanut skin
Ergotamine tartrate	Ginkgo biloba L.
Scopolamine hydrobromide	Cordia verbenacea
Digoxin	Nicotine
Curcumin	Zingiber officinale
Quercetin	Mangifera indica
Resveratrol	Propolis
Caffeine	Emblica officinalis
Enterococcus faecium CRL183	Olive leaf
Quinine hydrochloride	Acerola powder
Nicotine	Neem
Caffeine anhydrous	Myrrh

2. Film-forming polymers

The most important significant element for the effective design of oral thin film formulation is the selection of film-forming polymers.[6] For the development of oral disintegrating film, a range of film-forming polymers are available, which are utilized at a concentration of around 40-45 % w/w of total film weight, but can be raised to 65 % w/w of film weight alone or in combination to achieve desirable oral film qualities.[2]

Characteristics of polymer

- It should be tasteless, non-toxic and non-irritant.[6]
- It should possess good shelf life.[3]
- It should not cause infection in the buccal cavity.

Recently at this time, both natural and synthetic polymers are utilized to make oral thin films.[6] Table 3 lists the natural and synthetic polymers.

Table 3: Natural and synthetic polymers[4, 6, 12]

Natural Polymers	Synthetic Polymers
Pullulan	Hydroxypropyl cellulose (HPC)
Sodium alginate	Hydroxypropyl methylcellulose
Pectin	Sodium carboxymethylcellulose
Gelatin	Polyvinyl alcohol
Maltodextrin	Polyethylene oxide
Starch	Polyvinyl pyrrolidone
Gum acacia	

METHODS USED FOR FORMULATION OF OFDF

A) Conventional Methods

To prepare OFDFs, one or a combination of the following traditional methods can be employed.[15]

1. Solvent casting method

Hydrophilic polymers are dissolved in water at 1000 rpm and heated to 60 °C in this technique. After that, all of the additional excipients are dissolved independently. The two solutions are then completely combined while rotating at 1000 rpm. The active phytochemical ingredient is dissolved in a suitable solvent and added to the resulting solution. The resultant solution is then cast as a film and allowed to dry before being cut into appropriate size pieces.[3, 6, 16]

2. Semisolid casting

When the film constituent is an acid-insoluble polymer, this approach is favored. The first step is to dissolve water-soluble polymers in water. The resulting solution is then mixed with the acid-insoluble polymer solution that has been prepared separately. Both solutions have been thoroughly combined. Following the mixing of the two solutions, a sufficient quantity of plasticizer is added to the final solution to get the gel's mass. Finally, heat control drums are used to cast the gel mass onto the films or ribbons. The film thickness should be between 0.015 and 0.05 mm. The acid-insoluble polymer should be used at a 1:4 ratio with the film-forming polymer. Cellulose acetate phthalate and cellulose acetate butyrate are examples of acid-insoluble polymers.[6]

3. Hot melt extrusion (HME)

In contrast to the solvent casting method, HME is a solvent-free process that uses heat to produce the films. A screw extruder heats and homogenizes the excipients and API until they are completely mixed. The mixture is extruded via a flat extrusion die, which forms the extrudate into the appropriate film shape. It is then cooled, trimmed to size, and packed.[17]

4. Solid dispersion extrusion

The purpose is to diffuse the active ingredient into a melted polymer solution so that it may be loaded more easily. There can be one or more active ingredients that are dissolved in a suitable liquid solvent that functions as an inert carrier. This occurs in the presence of an amorphous hydrophilic polymer at 70°C without the requirement to remove the liquid solvent in order to get the solid dispersion required. Finally, the dyes are used to form the solid dispersions into films.[4]

5. Rolling method

The film is first formed by premix preparation, then combined with drug solution and put to the roller in the rolling procedure. Film-forming polymers, solvents, additional ingredients and additives make up the premix, but no active ingredient is included. The premix is poured into the masterbatch tank, which is then fed by a first metering pump and controlled by one or both of the first and second mixers.[18] After that, the needed amount of active component is added to the desired mix, which is then blended with the masterbatch premix to create a consistent matrix. Second metering pumps provide a certain quantity of homogeneous matrix to the pan, and the film is eventually created and dragged away by a support roller, and the wet film is subsequently dried using controlled bottom drying.[4]

B) Patent Approaches:[1]

Bio-progress has created some thin film manufacturing technologies, which are mentioned below.

1) SoluleavesTM

- FoamburstTM

2) XGelTM

3) WaferTabTM

CURRENT RESEARCH ON PHYTOCHEMICAL LOADED OFDFs

Recent studies show that phytochemicals produce a wide range of therapeutic effects and help in the management of certain disorders. Phytochemicals such as flavonoids, polyphenols, glycosides, saponins, etc. and active constituents present in them are employed in the formulations. Phytochemicals can be incorporated in the formulation and development of OFDFs to produce pharmacological activities. Recent research and studies showed a significant therapeutic role of phytochemicals in OFDF formulation when integrated as an active ingredient. In recent years, researchers have developed OFDFs by incorporating active phytoconstituents and/or herbal extracts to produce significant therapeutic activity. Active phytoconstituents such as quercetin, herpetrione, curcumin, etc. can be formulated with film-forming polymers and other ingredients to obtain oral thin film. Certain herbal extracts of peanut, propolis, olive leaf, etc. can also be used as natural active compounds in the formulation and development of OFDFs for therapeutic roles. The extracts are obtained by several extraction techniques such as ethanol extraction, bleaching, decoction and maceration. These natural active compounds have anti-inflammatory, antiviral, immunomodulatory, antimigraine, antiarrhythmic, antioxidant and antibacterial activities. Phytochemical-based OFDFs can be used in the management of Alzheimer's disease, dementia and cerebral insufficiency. Researchers have developed many OFDFs using phytochemicals as an active ingredient. Table 4 displays a brief data of various researches carried out on phytochemical integrated OFDFs.

Table 4: Recent research on phytochemical loaded OFDFs

DT- Disintegration time, T- Thickness, DC- Drug content, TS- Tensile strength

Phyto-constituents	Other Ingredients	Characterization of films	Role of phytochemicals
Active Phytoconstituents			
1) Herpetrione[19]	Sodium dodecyl sulfate, Kollidon, HPMC, Microcrystalline cellulose, PEG-400	DT: 20 sec T: 0.11-0.12 mm	Antiviral activity
2) Caffeine[20]	HPMC 2910, Sodium alginate, Sodium starch glycolate, Kollicoat, Citric acid anhydrous, Glycerin, Sucralose	DT: 12-45 sec T: 0.048-0.188 mm	Immunomodulatory and CNS stimulatory activity
3) Caffeine anhydrous[21]	HPMC E-15, Dichloromethane	DT: 17.5-38.4 sec T: 0.025-0.057 mm	Supplement for weight loss
4) Ergotamine tartrate (ET)[21]	HPMC E-15, Dichloromethane	DT: 136.4-167.36 sec Surface pH: 5.46-5.87	Antimigraine activity
5) Curcumin[22]	HPMC, Glycerin, Sorbitol, Tween, Span	DT: 46.99-92.7 sec T: 0.08 mm DC: 94.51-98.22%	Anti-inflammatory, anticancer, antidiabetic
6) Curcumin[23]	PEG-4000, Polyvinyl pyrrolidone k30, Lycoat RS720, Glycerin	DT: 45-95 sec T: 0.06-0.91 mm DC: 98.11-101.09%	Targeted condition: Mouth ulcers
7) Digoxin[24]	Sodium alginate, Zein nanoparticles, Glycerol	DT: 6.09-12.04 sec T: 0.08-0.11 mm	Antiarrhythmic activity
8) Nicotine[25]	Maltodextrin, Nicotine hydrogen tartrate salt, Sorbitan oleate	T: 0.11-0.14 mm	Smoking cessation
9) Nicotine hydrogen tartrate[26]	HPMC E3 LV, HPMC E5 LV, PEG 400	DT: 12.18-119.34 T: 0.149-0.165 mm TS: 9.11-26.28 kg/mm2	Smoking cessation
10) Vaccinium Oxycoccos and Plectranthus Amboinicus[27]	HPMC, citric acid, Aspartame	DT: 120-240 sec Surface pH: 6-7	Targeting Streptococcus Mutans
11) Scopolamine hydrobromide[28]	Pullulan, HPMC E15, PEG	DT: 8-13 sec T: 0.19-0.32 mm	Anti-sialagogue activity in dentistry to minimize chair time needed for dental

		Surface pH: 6.9-7.2	procedures.
12) Resveratrol[29, 30]	1) Poloxamer 188, PVA, Glycerin	DT: 28.34-34.70 sec T: 0.01-0.1 mm TS: 9.13-11.02 MPa	Antioxidant activity
	2) HPC, Ethyl cellulose, PEG 400	DC: 90.29-100.9% Surface pH: 5.39-7.15	Anti-inflammatory, chemo-preventive effects
13) Quercetin[31, 32]	1) Maltodextrin, Glycerin	T: 0.016 mm TS: 0.49-0.57 MPa % Elongation: 85-166%	Antibacterial activity
	2) HPMC K-15, Carbopol 940, Glycerin, Tween 80	T: 0.04-0.08 mm DC uniformity: 0.022-0.023	Antibacterial
14) Quinine hydrochloride[33]	Pullulan, HPMC, HPC, PVP	DT: 19.1-149.4 sec T: 0.035-0.08 mm DC: 3.08-3.5 mg/strip	Muscle relaxant
15) Enterococcus faecium CRL183[34]	CMC, Gelatin, Potato starch	DT- 1.28 min- 6.43 min T- 0.08-0.1 mm	Antifungal (anti-candida albicans)
Herbal Extracts			
1)Peanut skin extract[35]	Gelatin, HPMC E15, Sorbitol	DT: 16.96-27.41 sec T: 0.05 mm Surface pH: 6.36-6.88	Antioxidant activity
2) Ginkgo biloba L. Extract[36]	CMC, PEG, Glycerol, Arabic gum	DT: 99-101 sec T: 0.05mm TS: 48-54 MPa % Elongation- 3.4-3.8% Young's Modulus- 3189-3211 Mpa	Anti-inflammatory, antioxidant, analgesic, anti-asthmatic
3) Cordia verbenacea (erva baleeira) extract[37]	Starch, HPMC, Sorbitol	DT: 20.3- 37.2 sec T: 0.06 mm TS: 9.5-12.1 MPa % Elongation- 2.2-3.4%,	Antioxidant and anti-inflammatory activity
4) Nicotine extract from tobacco leaves[38]	HPMC E15	DT: 18.40-20.5 sec T: 0.07 mm TS: 6.92-7.54 N/mm2 Elongation break- 7.73-7.89%	Smoking cessation
5) Zingiber officinale extract[39]	Maltodextrin, Pullulan, HPMC 5, PVA, PEG, Polysorbate	DT: 24.65-25.35 sec T: 0.05-0.07 mm Folding endurance: 192.14-351.46	Appetite stimulatory and anti-inflammatory activity
6) Mangifera indica extract[40]	Corn starch, Glycerol	DT: 20.5-41.8 Surface pH- 6.65-7.65	Antioxidant activity
7) Propolis extract[41]	Porcine gelatin type A, Hydrolyzed collagen, Sorbitol	T: 0.062-0.072 mm TS: 23.9-33.0 MPa % Elongation: 33.0-50.0%	Antimicrobial activity against Staphylococcus aureus
8) Emblica officinalis aqueous extract[42]	HPMC E50, PEG 400, Glycerol, Sodium sorbitol	Drug release: 100% in 30 min	Antibacterial activity

		TS: 86.8-107.75 N/cm2	
9) Olive leaf extract[43]	Dried okra, Carboxymethyl chitosan	DT: 5-30 sec T: 0.038-0.048 mm	Antioxidant activity
10) Acerola powder[44]	Maltodextrin, Sorbitol, Gelatin, Starch	DT: 6-11 sec Surface pH: 5.6-5.8	Anti-inflammatory
11) Neem extract[45]	Methyl cellulose, HPMC, Propylene glycol	T: 0.11 mm Drug diffusion: 27.08-35.21% in 30 min	Wound healer
12) Myrrh extract[46]	Sodium carboxy methylcellulose, HPMC K4M, Tween 80, PVP, Propylene glycol	T: 0.19-0.28 mm % Elongation- 23.34-25.22%	Antimicrobial agent

Conclusion

Oral fast disintegrating film (OFDFs) is a novel approach in the oral drug delivery system that fulfills an unmet need in a wide range of populations, including children, paralyzed, nauseated, and non-compliant patients. There is no need for water, measurement and after disintegration; the drug gets absorbed in oral mucosa providing quick onset of action. Phytochemical incorporated thin films can be formulated and used in the management of CNS-related diseases or disorders. Active phytoconstituents have a wide range of therapeutic roles. The drug loading is restricted to roughly 30 mg, so the drug to be integrated into the film formulation should be highly potent.

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