Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Review
Volume 13, Issue 2, 2023, 177
https://doi.org/10.33263/BRIAC132.177

Oral Thin-films from Design to Delivery: A Pharmaceutical Viewpoint

Manasa Chandramouli [1], Rajendra Prasad Shivalingappa [2], Vrushabendra Basavanna [1], Shridevi Doddamani [3], Dileep Chikkur Shanthakumar [4], Sandhya Rani Nagarajaiah [4], Srikantamurthy Ningaiah [1,*]

[1] Department of Chemistry, Vidyavardhaka College of Engineering, Visvesvaraya Technological University, Mysore-570 002, Karnataka, India
[2] PG Department of Chemistry, Davangere University, Shivagangothri, Davangere-577007, Karnataka, India
[3] Chemical Sciences and Technology Division, CSIR-NIIST, Thiruvananthapuram-695 019, Kerala, India
[4] Department of Physics, Vidyavardhaka College of Engineering, Visvesvaraya Technological University, Mysore-570 002, Karnataka, India
* Correspondence: srijmn@vvce.ac.in (S.N.);

Scopus Author ID 55786395000
Received: 12.02.2022; Accepted: 13.02.2022; Published: 30.03.2022

Abstract: Stable drug-type tablets and capsules are painful to drink or chew for many pediatric and geriatric patients. Accurate dosing is also an issue for liquid orals (syrup, suspension, emulsion, and so on). Several fast-dissolving drug delivery systems have been designed to address these issues. One of the innovative methods for rapid drug delivery with self-administration without water or chewing is a thin polymer oral drug strip. Strip-forming polymers, plasticizers, active pharmaceutical ingredients, sweetening agents, saliva enhancing agents, flavoring agents, coloring agents, stabilizing and thickening agents are all used to form oral drug strips. The scope of oral thin films is expanded in this article.

Keywords: oral thin-films; capsules; liquid orals; self-administration.

1. Introduction

Based on the transdermal patch technologies, the oral thin film is a modern method for oral drug delivery [1]. The distribution mechanism consists of a very thin oral strip that is mounted on the patient's tongue or some other oral mucosal tissue. As the film is wet with saliva, it quickly hydrates and adheres to the application spot. It quickly degrades and dissolves to release the medication for oromucosal absorption [2].

Based on the total weight of the dry film, at least 45 percent w/w of polymer should be present. The strip's toughness is determined by the type of polymer used and the volume used in the formulation. The film you receive should be durable enough to withstand handling and shipping without being damaged.

Thin and stable dosage formulations that dissolve in the mouth in seconds are known as mouth dissolving films [3]. Pediatric and geriatric patients who have trouble swallowing conventional oral solid-dosage types are pills, capsules, and syrups. Since the oral and buccal mucosas are highly vascularized, medications can penetrate immediately and enter the systemic circulation without passing through the digestive system [4].

These films make it easy to administer drugs to children, the elderly, and bedridden patients. Good taste, high stability, and ease of handling are all desirable qualities in a film [5]. A solid dosage medium is a fast-dissolving oral thin film (FDF); when inserted in the mouth without water or chewing, OTFs disintegrate or dissolve in 1 minute [6]. Pre-gastric absorption from the mouth, pharynx, and esophagus as saliva flows down into the stomach increased the drug's therapeutic effect as it disintegrated in the mouth [7]. Adhesive tablets can be favored by fast-dissolving films concerning their flexibility and comfort [8]. For the preparation of FDF, several polymers are available [9]. Polymers, active pharmaceutical additives, film stabilizing agents, sweeteners, flavors, textures, saliva-inducing agents, preservatives, surfactants, and other ingredients are used in the film's preparation, but the first and most important ingredient that aids in film-forming is a polymer. The three types of quick dissolve technologies are oral thin films, compressed tablet-based applications, and lyophilized devices [10].

2. The Lyophilized Devices

The technology behind these systems entails shaping tablet-shaped units from a suspension or solution of a drug with other structural excipients using a mold or blister kit. Following that, the units or tablets are frozen and lyophilized in a pack or mold. The resulting units have high porosity, enabling rapid water or saliva penetration as well as fast disintegration [11].

3. Compressed Tablet-based Systems

This device is developed by compressing excipients directly using normal tablet technology. Tablet technologies vary in terms of stiffness and friability depending on the manufacturing process. As opposed to a normal tablet, fast-dissolve tablets are made with water-soluble excipients or super-disintegrant or effervescent components to enable rapid water penetration into the interior of the tablet [12].

4. Oral Thin Films (OTF)

Oral films also referred to as oral wafers in the literature, are a form of flat film placed in the mouth [13]. Dissolvable oral thin films (OTFs) or oral strips (OS) emerged from the confection and oral care industries in the form of breath strips over the last few years and have become a new and generally recognized form of supplying vitamins and personal care products [14]. OTFs are now a well-established and widely used technology for the systemic delivery of APIs in over-the-counter (OTC) products, and they are in the early stages of growth for prescription drugs. This is partially due to the popularity of commercial air freshener products in the United States, such as Listerine Pocket Packs [15]. To generate a 50-200 mm film, these devices use a variety of hydrophilic polymers [16]. According to reports, this film can contain soluble, insoluble, or taste-masked drug compounds. The film is made as a large sheet, then sliced into individual dosage units and packaged in several pharmaceutically appropriate formats [17].

5. The Use of Oral Films for Drug Delivery

Oral uses: Oral mucosal distribution through buccal, sublingual, and mucosal routes using OTFs could become the preferred delivery method for therapies that need rapid absorption, such as discomfort, asthma, sleep issues, and central nervous system disorders.

Topical uses: Using dissolvable films to distribute active agents such as analgesics or antimicrobial additives for wound treatment and other applications [18].

Gastro retentive dosage systems: Dissolvable films are being considered for dosage forms that contain water-soluble and poorly soluble molecules of different molecular weights in a film format. The films' breakdown could be caused by the gastrointestinal tract's pH or enzyme secretions, which could be used to treat gastrointestinal disorders [19].

Diagnostic devices: Dissolvable films can be filled with sensitive reagents to enable controlled release when exposed to biological fluids, or they can be used to establish separation barriers between several reagents to allow a timed reaction within a diagnostic system [20].

Fast dissolving drug delivery systems were first introduced as an alternative to traditional medication formulations in the late 1970s. Orally disintegrating tablets (ODTs) and oral thin films are examples of fast dissolving products (OTFs) Zuplenz (Ondansetron hydrochloride - 4 mg, 8 mg) (Figure 1a) was the first opioid OTF to be approved in 2010. Suboxone (buprenorphine and naloxone) was immediately approved for the second time (Figure 1b & cc). Oral thin film drug distribution systems that dissolve easily are a safer alternative to ODTs. When OTFs are put on the tip or the floor of the tongue, saliva immediately wets them. OTFs hydrate quickly before dissolving and/or dissolving to release medication.

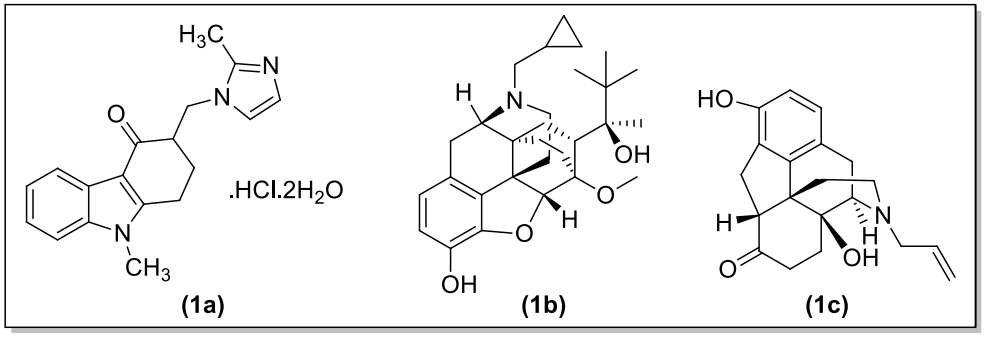

Figure 1. Opioid OTF.

Because of the convenience of absorption, pain avoidance, and versatility, the oral route is the most favored route for medication distribution. Since they are afraid of choking, many pediatric and geriatric patients refuse to make firm preparations. According to one study, 26 percent of 1576 patients had problems swallowing pills. Tablet size was the most common concern, followed by surface shape and flavor. There has been an enhanced demand for more patient-compliant dosage forms for the last two decades.

Oral films are flexible and thus less fragile than ODTs, making them easier to transport and store [21]. Drugs can be absorbed directly and enter the systemic circulation without undergoing first-pass hepatic metabolism. Oral dissolving tablets (ODTs) are sometimes difficult to carry, store and handle (fragility and friability).

It is helpful since it is used to relieve pain, cough/cold, gastroesophageal reflux disease, erectile dysfunction, sleep disturbances, and sleep apnea in pharmaceuticals, Rx prescriptions, and over-the-counter medicines. Since it disintegrates and dissolves quickly, it can increase bioavailability for poorly water-soluble drugs. It is possible to produce and ship a product in

12-16 months, resulting in a shorter product production life cycle. In liquids, it has strong chemical stability and chemical integrity. To aid in product growth, it provides business extension and product differentiation.

It is a significant threat because testing has shown that the concentration of active pharmaceutical ingredients (API) can be increased by up to 50% w/w. Gas-X® thin strips from Novartis Consumer Health contain 62.5 mg of Simethicone (Figure 2). Since OTFs melt instantly, it is difficult to stop taking them. Active pharmaceutical ingredients with high doses are not appropriate candidates for insertion into quick-dissolving oral thin films since the thin films must be compact enough to be put on the tongue comfortably [22] [Active pharmaceutical ingredients (APIs)].

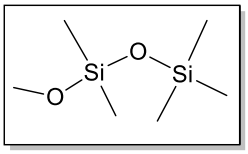

Figure 2. Structure of Simethicone.

Therefore, the following characteristics are good for an ODT: Low dose, palatability, small molecular weight, and solubility and stability in saliva.

OS technology can offer a wide range of APIs [23]. It's impossible to integrate high-dose molecules into OS. Many APIs that could be used in OS technologies have a sour taste to them. This makes the formulation unappealing, especially in pediatric formulations. For prompt relief, such pathologies necessitate the instantaneous release of the medication. For example, in the case of migraines, a rapid therapeutic result is needed by the patient. Sore throats, coughs, allergies, and other local oral manifestations would necessitate regimen-specific distribution. Micronized API is often helpful because it increases the texture of the film.

Water-soluble APIs can be used dissolved or as a solid solution, and distribution uniformity is not an issue. However, to achieve sufficient medication quality uniformity, water-insoluble APIs must be delivered uniformly. To preserve the smooth texture of the film and also for fast dissolution, water-insoluble APIs may be applied as milled, micronized, nano-crystals, or microcapsules [24].

Drugs having a bitter and unpleasant taste may cause a vomiting sensation and maybe unacceptable to the patient. Various taste-masking technologies for the drug-like coating with polymers are being practiced.

5.1. Polymers that shape films.

The film-forming polymers must be water-soluble since the film composition quickly disintegrates and dissolves in the oral cavity. The type and amount of polymer used in the mixture determine the film's toughness. The molecular weight of polymer film bases is increased, which increases the disintegration time of the polymers. Since polymers and APIs are such essential components of the film composition, their proportions are determined by two factors:

a) Minimum percent weighted average polymer concentration needed to shape matrix incorporating APIs and other excipients with desired mechanical and viscoelastic properties.

b) The viscosity of the liquid should be about right to keep suspended solids from settling.

Polymers should ideally be non-toxic, non-irritant, bland, have a good mouthfeel, should be stable for long periods, should not alter properties of the active pharmaceutical ingredient or other excipients of the formulation, inexpensive, should have good wettability and spreadability, should not retard the disintegration time of the film, should have optimum peel strength and tensile strength.

5.2. Polymers.

5.2.1. Gum polysaccharides.

Any alternative polymers for film formulation are gum polysaccharides such as gum arabic and sodium alginate (Figure 3). They can be mixed with other materials to have a primary film structure and fast dissolving properties. The addition of these will increase film dissolution in the mouth and minimize tensile strength to a small degree.

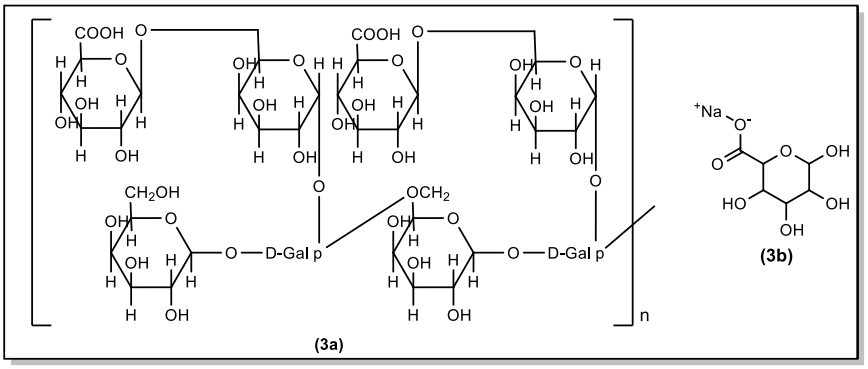

Figure 3. Alternative polymers (gum polysaccharides).

5.2.2. Gelatin.

Thermal denaturation of collagen isolated from animal skin, bones, and fish skins produces gelatin (Figure 4). Above 40°C, it dissolves readily in water and forms a viscous solution of randomly coiled polypeptide strands. Due to their higher amino acid content, mammalian gelatins have improved physical properties and thermostability than most fish gelatins. The properties and film-forming ability of gelatin are directly related to the molecular weight of the gelatin. Gelatin films have the following advantages: They dissolve quickly and have a soft mouth texture, making them excellent taste carriers.

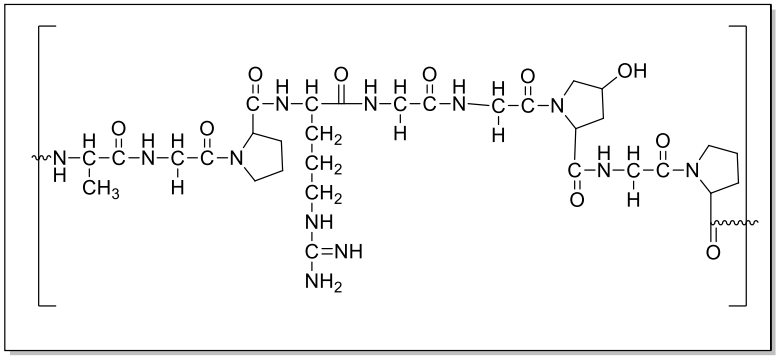

Figure 4. Structure of gelatin.

5.2.3. Pullulan.

Pullulan (Figure 5) is a neutral linear polysaccharide that is water-soluble. Aureobasidium pullulan, a black yeast, produces it from starch. Pullulanase hydrolyzes a

specific linkage pattern that gives it its special film-forming properties. With a molecular weight of 2,00,000 daltons, the PI-20 grade has outstanding film-forming properties. It can be used at a concentration of 0.3 to 15% w/w. Pullulan films are 300 times more resistant to oxygen than HPMC films. They're good for keeping readily oxidized fats and vitamins in a food safe. Pullulan is non-carcinogenic, non-toxic, non-immunogenic, and non-mutagenic. It's a nonionic polysaccharide that's compatible with blood and biodegradable. It has excellent adhesion and film formation properties. It is hygroscopic-free, translucent, and flexible.

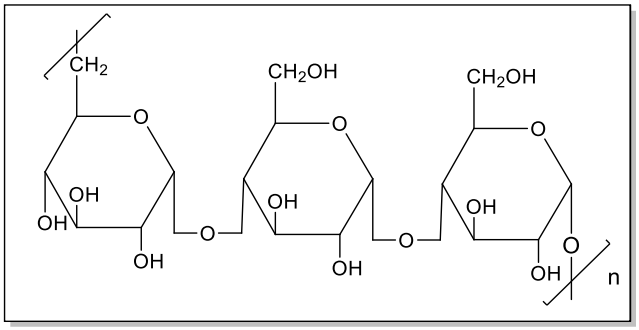

Figure 5. Structure of pullulan.

5.2.4. Starch.

In-plant tubers and seed endosperm, which are found as granules, starch (Figure 6) is the main carbohydrate reserve. Millions of amylopectin molecules coexist with smaller amylase molecules in each granule. Amylose is responsible for starch's ability to mold films. Biodegradable and translucent starch films are flavorless, tasteless, and colorless, and they are transparent. Because of its poor mechanical ability, film formation conditions affect the crystallinity and properties of starch films. Films made of high-amylose corn starch or potato starch were more durable over time, losing less elongation, and had little or no tensile strength rise. Because of its low cost, modified starch is often combined with pullulan.

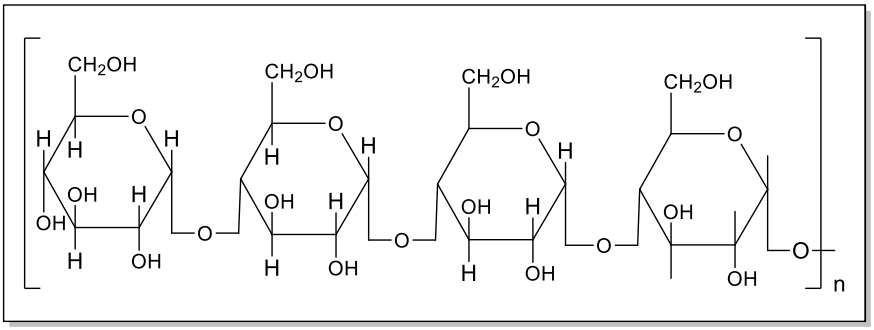

Figure 6. Structure of starch.

5.2.5. Lycoat.

Lycoat is a granular hydroxypropyl (Figure 7) starch polymer made from pea starch that was developed primarily for fast-dissolving oral thin films. Roquette Pharma is the organization that makes it. Lycoat disperses readily in cold water, leaving no lumps or clumps behind. It does not require the use of organic solvents to form films. It has a neutral flavor and can be loaded as a crystalline powder or dissolved in an organic solvent. It can be used without adding a film-forming agent to produce quick-dissolving oral thin films with excellent functionality.

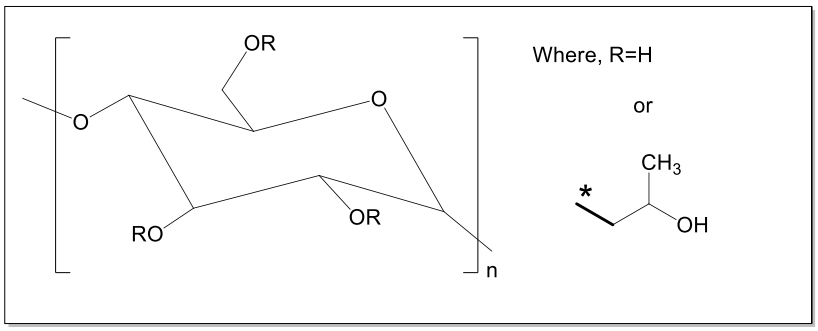

Figure 7. Structure of lycoat.

5.2.6. Maltodextrin.

Maltodextrin (Figure 8a) is a nutritive saccharide polymer that isn't good. It's created by partly hydrolyzing starch. It is made up of D-glucose (Figure 8b) units linked together in chains of varying lengths. DE (dextrose equivalent) is used to identify maltodextrins, and DE varies from 3 to 20.

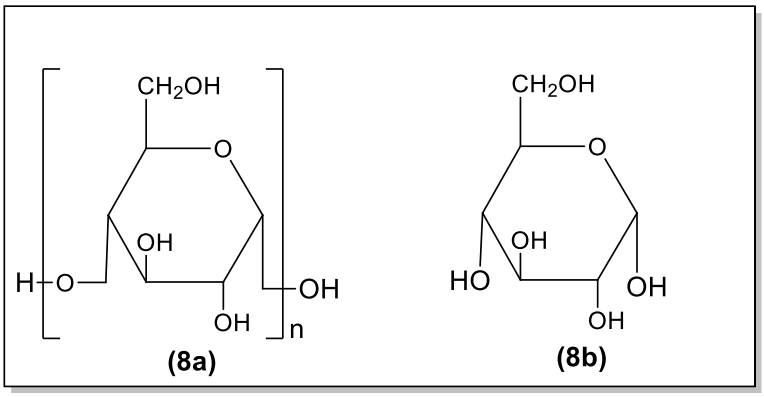

Figure 8. Maltodextrin and its unit.

5.2.7. Hydroxypropylmethylcellulose (HPMC).

HPMC, or hypromellose (Figure 9a), is cellulose (Figure 9b) that has been partially O-methylated and O-(2-hydroxypropylated). Because of their low viscosity, lower grades of HPMC, such as HPMC E3, HPMC E5, and HPMC E15, are especially useful for film formulation [48]. The aqueous solution is used for lower grades. For film-forming solutions, concentrations of 2-20 percent w/w are used, depending on the viscosity grades. To boost certain properties, additives are used. Several experiments have been performed to see how additives affect the Physico-chemical properties of HPMC films. In aqueous solutions, HPMC shapes clear, rugged, and versatile films. It has outstanding acceptability and film-forming properties.

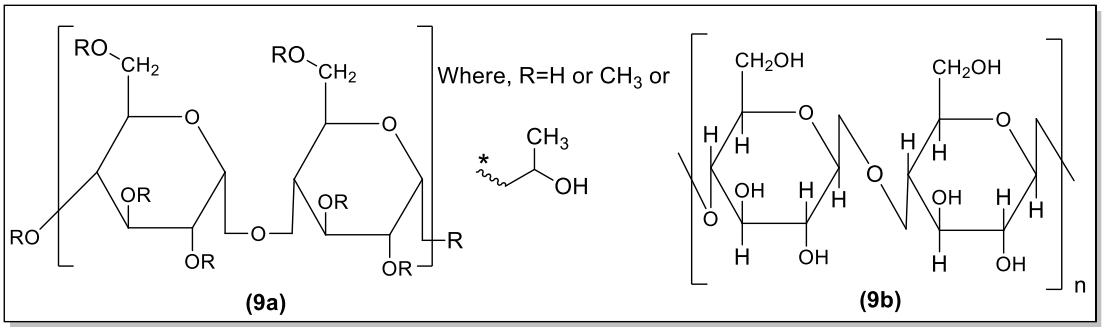

Figure 9. Hydroxypropylmethyl cellulose and its unit.

5.2.8. Polyvinylalcohol (PVA).

A polyhydroxy polymer, poly (vinyl alcohol) (PVA) (Figure 10a), is a synthetic, water-soluble polymer made commercially by the hydrolysis of poly (vinyl acetate) (PVAc) (Figure 10b). PVA is typically plasticized by low molecular compounds, most of which contain polar groups, which form hydrogen bonds with the hydroxyl groups of the PVA chain (with or without water assistance). PVA is a good film-forming and emulsifying material. It is odorless, non-toxic, and oil and grease-resistant. It has sufficient tensile strength as well as acceptable flexibility. It is non-toxic and biodegradable, with high oxygen and scent barrier properties.

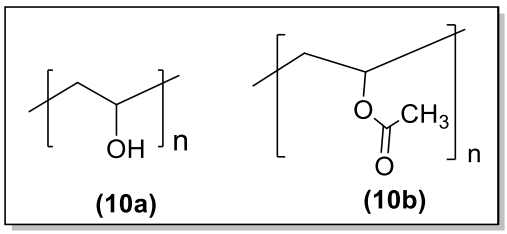

Figure 10. Polyvinyl polymer.

5.2.9. Polyethylene oxide (PEO).

A plastic polyether is polyethylene oxide (Figure 11). It comes with a wide variety of molecular weights. Film formulation is usually done with a 3-5 percent w/w solution. Glass has a high melting point and is highly structurally sound. Glass is biocompatible and has low toxicity. It has high hydrophilicity and a high film-forming capability.

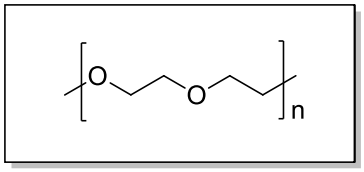

Figure 11. Polyethylene oxide.

5.2.10. Polyvinyl pyrrolidone (PVP).

The radical polymerization of N-vinyl produces soluble polyvinyl pyrrolidone (Figure 12). The PVP collection contains items of multiple K-values. Kollidon® is the brand name for soluble PVP materials. Water and most other solvents are easily soluble in PVP. It is chemically inert and non-toxic. PVP is colorless, temperature tolerant, and pH stable. It has a high potential for film creation.

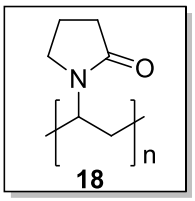

Figure 12. Polyvinyl pyrorolidone.

5.2.11. Sodium alginate.

Since alginate (Figure 13) is an indigestible biomaterial formed by brown seaweeds (Phaeophyceae, mostly Laminaria), it can be considered a source of dietary fiber. Because of their hydrophilic nature, edible films made from alginate form solid films with low water

resistance. Edible films made of alginate are ideal for storing additives and antibacterial compounds. The permeability of water and mechanical attributes can be considered moderate compared to synthetic films.

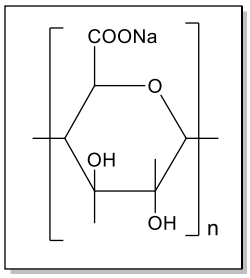

Figure 13. Sodium alginate.

5.2.10. Pectin.

Fruit and vegetable pectin (Figure 14a) is a heterogeneous grouping of acidic structural polysaccharides. HMP or LMP type excellent films with Chitosan (Figure 14b). When a pectin-containing edible film was used to inhibit crumb aging of a dietetic sucrose-free sponge cake, crumb aging was prevented. This sponge cake kept its freshness better, particularly up to the fifth day of storage.

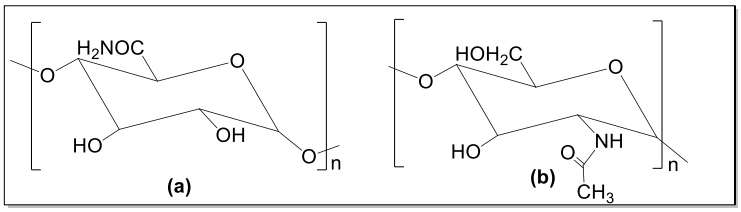

Figure 14. Pectin and Chitosan.

5.2.11. Rosin.

Because of its origin in Colophon, an ancient Ionic city, rosin (Figure 15) is also known as colophony or colophonia resina. It is a thermoplastic, acidic substance made from live pine tree exudates. Different specimens have different physical melting points, with others being semi-fluid at boiling water temperature and others melting at 100°C to 120°C. The plasticizer-free solutions created smooth, clear, yet brittle films. Plasticizers have a significant impact on the efficiency of film coating, resulting in a reduction in tensile strength.

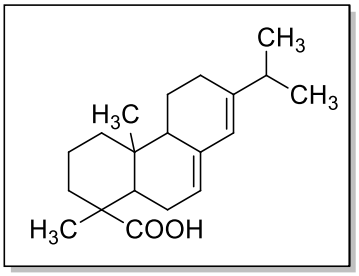

Figure 15. Rosin.

5.2.12. Chitosan.

After cellulose (Figure 9b), chitosan (Figure 14b) is the second most available natural and non-toxic polymer. Chitosans have a low solubility in neutral liquids, which is a downside. The viscous substance, which resembles natural gums, is primarily constructed from crustacean

shells. Pure chitosan films are normally cohesive, lightweight, and have a smooth contour on the surface.

5.2.13. Kollicoat.

Kollicoat (Figure 16a) is polyvinyl alcohol (Figure 16b) polyethylene glycol (Figure 16c) graft copolymer that was formulated specifically as a coating polymer for instant release formulations. The polyvinyl alcohol moiety has excellent film-forming properties, whereas the polyethylene glycol component is an internal plasticizer. In addition, since the molecule is hydrophilic, it dissolves easily in water.

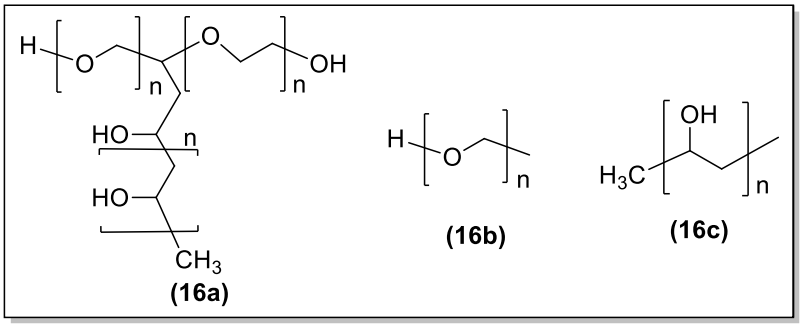

Figure 16. Kollicoat.

5.2.14. Plasticizers.

By lowering the polymer's glass transition temperature, plasticizers such as DEHP (Figure 17a) help improve the stability and brittleness of the film. The plasticizer must be compliant with the polymer as well as the solvent. Plasticizers used inappropriately or unnecessarily can cause film cracking, fracturing, and peeling. In addition, some plasticizers affect the drug's absorption rate. Plasticizers containing hydroxyls, such as polyethylene glycol, propylene glycol (Figure 17b), glycerol (Figure 17c), and polyols (Figure 17d), were used to plasticize cellulosic hydrophilic polymers quickly. On the other hand, less hydrophilic cellulosic polymers are plasticized with citric acid (Figure 17e) and phthalic acid esters (Figure 17f). Glycerol is a stronger plasticizer for polyvinyl alcohol. At the same time, diethylene glycol (Figure 17g) can be used for hydroxypropyl methyl cellulosic and hydroxyl propyl methyl cellulose as well as polyvinyl alcohol films.

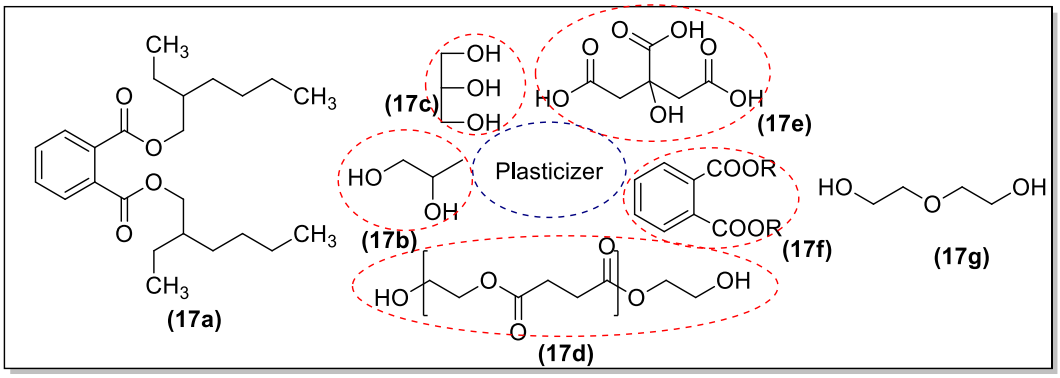

Figure 17. Plasticizers.

The plasticizer selected would be determined by its consistency with the polymer and the form of solvent used in strip casting. It aids in the improvement of strip flexibility and the reduction of strip brittleness. Plasticizer strengthens strip properties by decreasing the

polymer's glass transition temperature, which is in the range of 40–60 ºC for non-aqueous solvents and below 75 ºC for aqueous systems. Plasticizers are usually used at a concentration of 0– 20% w/w of the dry polymer weight.

5.3. Surfactants.

Surfactants function as wetting or dispersing agents, enabling the film to melt rapidly and release API. Surfactants, including sodium lauryl sulfate (Figure 18a) and polysorbates (Figure 18b), are widely used. Poloxamer 407 (Figure 18c) is an effective surfactant used as a wetting, solubilizing, and dispersing agent.

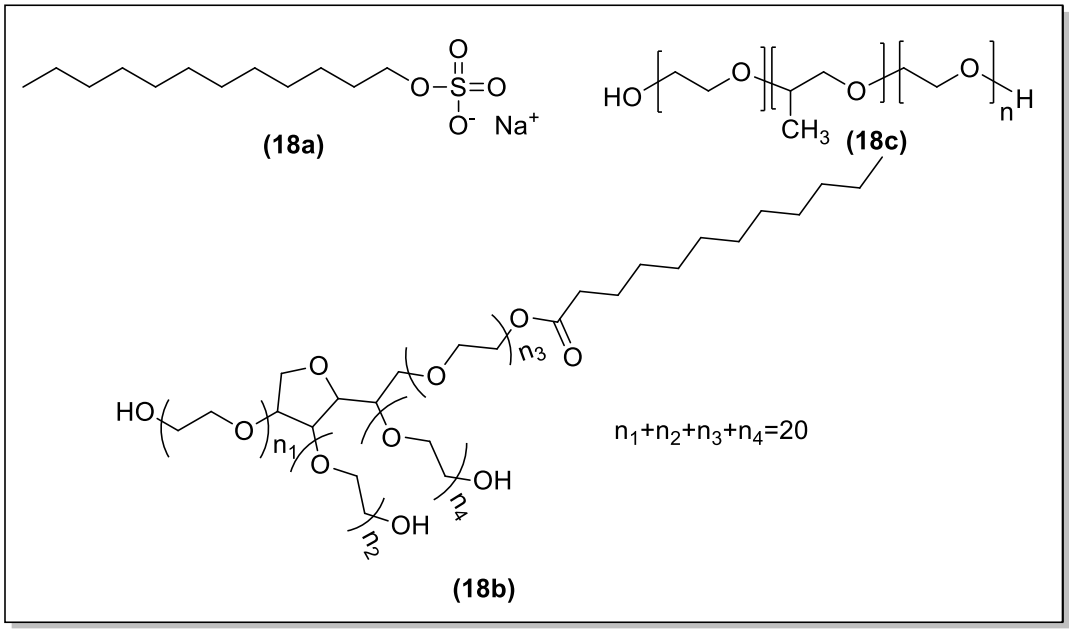

Figure 18. Surfactants.

5.4. Sweetening agents.

Sweeteners have been an integral component in nutritional and medicinal products meant to be disintegrated or dissolved in the mouth.

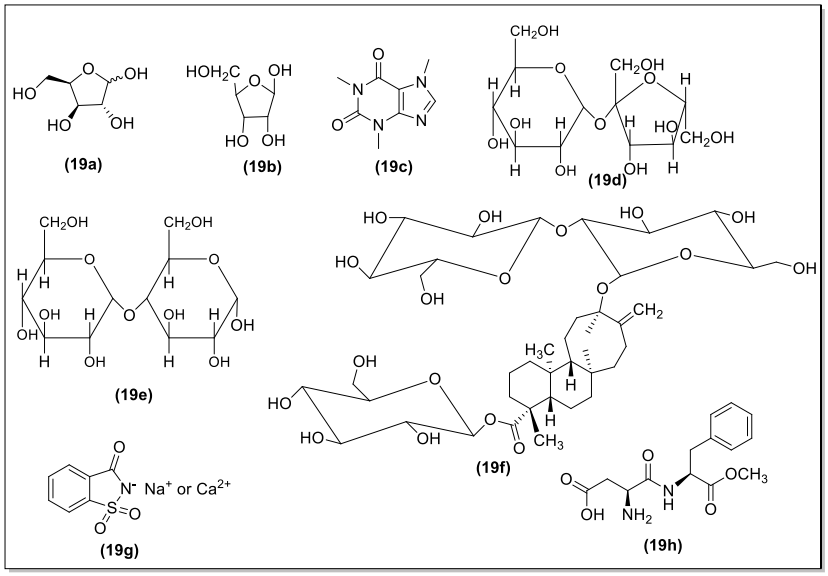

Figure 19. Sweetening agents.

In the case of children, the sweetness of the mixture is more important. To increase the palatability of the mouth dissolving preparations, natural and artificial sweeteners are used. Xylose (Figure 19a), ribose (Figure 19b), caffeine (Figure 19c), sucrose (Figure 19d), maltose (Figure 19e), stevioside (Figure 19f), and other sugars are suitable sweeteners. Sodium or calcium saccharin salts (Figure 19g) are water-soluble chemical sweeteners. Thaumatin I and II are protein-based sweeteners. Aspartame (Figure 19h) and other dipeptide-based sweeteners. In contrast to sucrose and dextrose, fructose is easily experienced in the mouth. Artificial sweeteners are favored by natural sugars because they require less concentration and do not induce dental caries.

To increase the palatability of the fast-dissolving oral thin films, both natural and artificial sweeteners are used. Sucrose, dextrose, fructose, glucose, and maltose are examples of sweeteners. Since fructose is sweeter than sorbitol (Figure 20a) and mannitol (Figure 20b), it is commonly used. Polyhydric alcohols are less cancer-causing and have no bitter aftertaste. Blending sweeteners will create harmony and enhance the taste. Compared to sucrose and dextrose, the sweetness of fructose is felt quickly in the mouth. Polyhydric alcohols like sorbitol, mannitol, isomalt (Figure 20c), and maltitol (Figure 20d) can be mixed because they have a nice mouthfeel and a cooling impact. But for xylitol (Figure 20e) and maltitol (both have sweetness similar to sucrose), the sweetness imparting property of most polyols is less than half that of sucrose. In the case of diabetic patients, the use of natural sugars in such preparations should be limited. Artificial sweeteners are becoming more common in food and pharmaceutical formulations as a result of this. The chemical sweeteners saccharin and aspartame belong to the first generation. These are carcinogenic, and several countries have banned them.

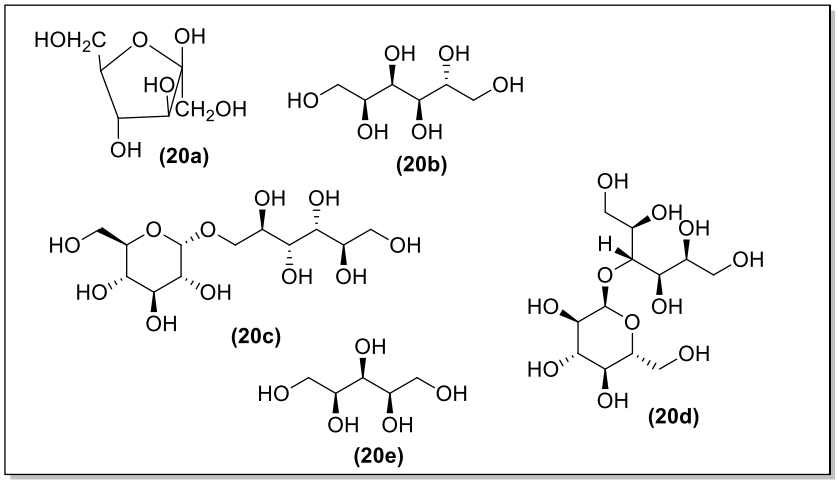

Figure 20. Sweetening agents.

Second-generation artificial sweeteners include acesulfame-K (Figure 21a), sucralose (Figure 21b), alitame (Figure 21c), and neotame (Figure 21d). Acesulfame-K and sucralose have sweetness ranges of over 200 and 600 times, respectively. When opposed to sucrose, neotame and alitame have a sweetening capacity of over 2000 and 8000 times, respectively. Rebiana is a herbal sweetener made from the Stevia (Figure 21e) rebaudiana plant. It has a sweetness of 200-300 times. Artificial sweeteners have the downside of having an aftertaste. Artificial sweetener disadvantages can be mitigated by mixing or combining natural and artificial sweeteners.

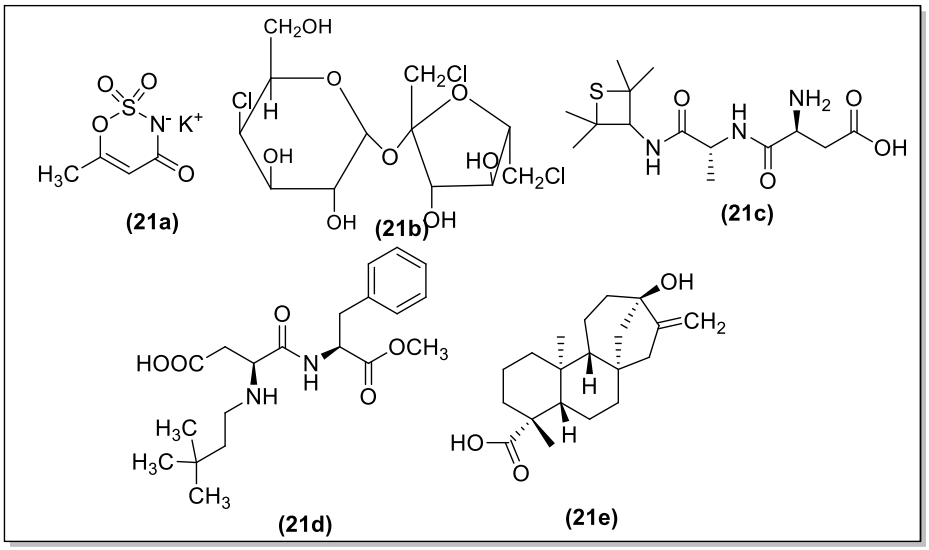

Figure 21. Second-generation artificial sweeteners.

5.5. Saliva stimulating agents.

Saliva stimulating agents tend to speed up the disintegration of formulations by increasing saliva intake. Saliva stimulating agents can usually be found in food-grade acids. Saliva relaxing agents include citric acid, malic acid (Figure 22a), lactic acid (Figure 22b), ascorbic acid (Figure 22c), and tartaric acid (Figure 22d). Citric acid is the most common and commonly used of all of them. These may be used separately or in tandem. The sum of resting and induced flow simultaneously under the same conditions can be used to assess salivation stimulation.

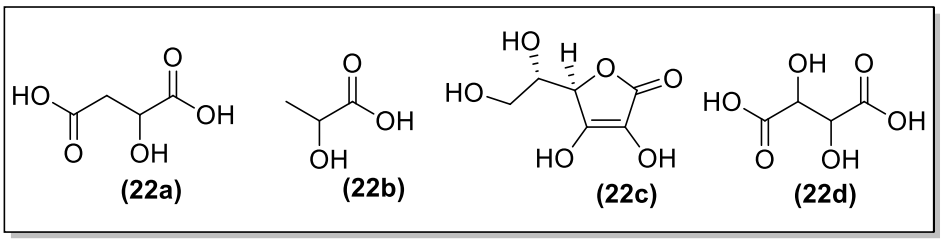

Figure 22. Saliva stimulating agents.

The aim of using saliva stimulating agents is to increase the rate at which saliva is produced. Salivary stimulants are used individually or in conjunction in amounts ranging from 2% to 6% of the strip's weight. Acids that are commonly used in food processing may be used as salivary stimulants.

5.6. Super disintegrants.

When super disintegrants are applied to a formulation, they cause rapid disintegration due to the combined effect of swelling and water absorption. Super disintegrants absorb water and swell, increasing dispersibility and improving disintegration and dissolution. For disintegration, strong interaction with water is necessary. The disintegration mechanism requires swelling, wicking, deformation, or combinations of any.

5.7. Colouring agents.

Up to 1% w/w of FD&C licensed coloring agents, EU colors, natural coloring agents, or pigments may be used. FD&C Yellow #6 was used as a coloring agent in the Nicotine (Figure 23) orally disintegrating film formulation, while titanium dioxide was used in the Ondansetron (1) Rapid Film formulation.

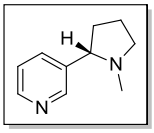

Figure 23. Nicotine.

5.8. Flavoring agents.

The type of substance to be added influences the taste choice. The initial flavor, is sensed in the first few seconds after the dosage product is absorbed. The after-taste of the formulation, which lasts for at least 10 minutes, determines an individual's approval of an oral disintegrating or dissolving formulation. Flavors should be used separately or in blends. Flavors of up to 10% w/w are preferred in the formulation. Flavor enhancers include menthol (Figure 24), chloroform, and certain salts. They have their distinct flavor and odor, as well as a slightly anesthetic effect on taste receptors.

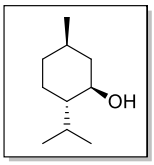

Figure 24. Menthol.

Perception of the flavors changes from individual to individual, depending upon ethnicity and liking. For example, the geriatric population likes mint or orange flavors, while the younger generation likes flavors like fruit punch, raspberry, etc. The acceptance of the oral disintegrating or dissolving formulation by an individual, by and large, depends on the initial flavor quality, which is observed in the first few seconds after the product has been consumed. Preferably up to 10% w/w flavors are added in the OS formulations. Synthetic flavor oils: Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg. Fruit essence type: Apple, raspberry, cherry can be used.

5.9. Cooling agents.

Cooling agents, such as monomethyl succinate (Figure 25), may be used to increase taste intensity and enhance the product's mouthfeel. Other cooling agents, such as WS3, WS23, and Utracoll II, can be used along with flavors.

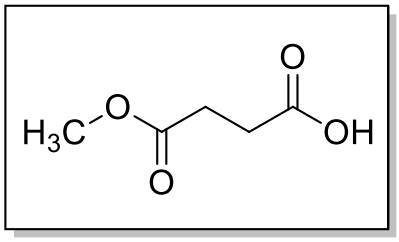

Figure 25. Monomethyl succinate.

5.10. Stabilizing and thickening agents.

Natural gums, such as xanthan gum, locust bean gum, carrageenan, and cellulosic derivatives, can be used up to 5% by weight. To boost strip properties, other additives such as surfactants and emulsifying agents are added in small amounts. Stabilizing and thickening agents are used to enhancing the viscosity and strength of the strip preparation solution's dispersion or suspension before casting.

6. Methods of Manufacturing

6.1. Solvent casting.

This is the most popular method for producing thin oral films that dissolve quickly. It involves the following, to make a viscous solution, water-soluble polymers are dissolved in water. Under high shear, other excipients and APIs are dissolved in an aqueous solution. The solution is cast into a film on a release liner with a thickness of 30-120 cm. Knife-over-roll, reverse roll, slot-die, gravure cylinder, and Mayer rod coating are examples of coating techniques. The film is dried in the oven before being cut into the desired form. The desired characteristics of the film product are investigated until it is packaged.

Water-soluble polymers are dissolved in water in the solvent casting process, while the medication and other excipients are dissolved in an appropriate solvent. All solutions are then combined and stirred before being cast onto Petri dishes, cleaned, and cut into standard dimensions.

Although different thicknesses can satisfy API loading and dissolution needs, the preferred finished film thickness is 12-100 μm. The solvents used to make oral thin films are selected from the ICH Class III solvents catalog.

Temperature for casting is between 20 and 90 ° C. Period to agitate: 40-120 minutes 1000-2000 RPM rotational speed. When defoaming, the flow rate is 80 liters per hour. During casting, the passage time is 2-8 minutes—temperature for drying: 50-130°C.

It is advantageous as the process is more cost-effective than hot-melt extrusion. It prevents APIs from being exposed to high temperatures, which can cause heat-sensitive APIs to degrade. The approach is also favored because it is more user-friendly. However, it is again disadvantageous as a volatile liquid or water must dissolve the polymer, and it is also necessary to provide an efficient approach with an acceptable viscosity.

The solvent-casting process is preferred for preparing the Refuse Derived Films, in which the water-soluble ingredients are dissolved to create a transparent viscous solution. The resulting solution is then cast as a film and dried before being cut into desired size sections. The choice of solvent is primarily decided by the API to be used in the strip.

6.2. Semisolid casting method.

The semisolid casting process begins with preparing a water-soluble film-forming polymer solution. The resultant solution is mixed with an ammonium or sodium hydroxide solution of an acid-insoluble polymer (e.g., cellulose acetate phthalate, cellulose acetate butyrate). After that, a suitable volume of plasticizer is used to create a gel mass. Finally, heat-controlled drums are used to cast the gel mass onto the films or ribbons. The film has a thickness of 0.015-0.05 inches. The acid-insoluble polymer can be used in a 1:4 ratio with the film-forming polymer.

6.3. Hot-melt extrusion.

By mixing API with excipients at a regulated temperature and steering speed, mass is produced. In the extruder, the mixture is molten. In a drying tunnel, the film is coated and cleaned. Slitting is finished, then pounding, pouching, and packing.

The drug is first combined with carriers in solid form in the hot-melt extrusion process. The mixture is then melted in an extruder with heaters—finally, the dyes from the melt into films.

15 rpm screw speed with a temperature for processing around 650°C to 1150°C. The final film thickness will be 200 μm with a temperature of extrudate around 650°C is the parameter for this particular method.

It is advantageous due to the following:

a) For drug handling, no solvent or water is used.
b) A decrease in the number of production steps.
c) A better option for poorly soluble medicines.
d) As compared to high shear approaches, less energy is required.
e) Because of the heavy mixing and agitation, the dispersion is more uniform.

There is also a possibility of thermal oxidation can where elevated temperatures are used, and also the polymer's flow properties are critical for manufacturing.

6.4. Solid dispersion extrusion method.

Immiscible components are extruded with the medication in this process, and stable dispersions are made. Finally, dies are used to transform the stable dispersions into films.

A fluid or suspension containing a substance is rolled on a carrier in the rolling process. Water and a combination of water and alcohol make up the rest of the solvent. The film is sliced into ideal forms after it has dried on the rollers.

6.5. Electrospinning.

Electrospinning (ES) is mostly used in the fiber and filtration industries. The procedure is to mix API with liquefied polymer and electrospinning the solution onto a collecting element. Electrostatic forces between the two electrodes draw fibers together, and the solvent evaporates, leaving solid nanofibers.

Due to its wide surface area, the electrospun polymer can disintegrate an aqueous medium in less than a minute. For use with various polymers, it has a wide range of flexibility.

6.6. Electrospraying.

For the preparation of OTFs, electrospraying is a relatively new process. Spraying a liquid under the influence of a heavy electric field is involved. The viscosity and particle/droplet size are the two main parameters influencing film characteristics. Electrospray can become electrospinning if the polymer content is too high.

Electrospinning and electrospraying are the recent technologies employed in the biofilms of oral dissolving strips.

6.7. Drying of films.

Drying assists in preserving the film's overall low temperature. The film interior cannot exceed the temperature at which the API degrades, even though the film surfaces are subjected to this temperature. The API does not degrade as a function of the temperature differential. The films are only allowed to dry for ten minutes or less. After a decent volume of the volatile solvent has evaporated, the film is exposed to heat again, causing uniform heat diffusion across the film and establishing the final shape. It can be desirable to shape a viscoelastic solid quickly. While small amounts of water can remain after the viscoelastic film is formed, the film can be dried further without losing its desired heterogeneity. After further drying, the final film is formed, with the solvent removed to the point that just around 6% of the solvent exists in the final film formulation.

7. Fast Dissolving Oral Thin Films Subjected to Various Evaluation Tests Differential Scanning Calorimetry

Scanning in Differential Mode Calorimetry is used to determine if a medication is compatible with other excipients. Differential Scanning Calorimetry may be used to test the plain medication and other excipients in the formulations. Film samples weighing around 5 mg are removed, sealed in aluminum pans, and tested at a 25 ml/min flow rate in a nitrogen atmosphere. A temperature range of 0 to 200 degrees Celsius is used.

7.1. Morphology studies.

Scanning Electron Microscopy is used to investigate surface morphology (SEM). It is possible to see pores, surface uniformity, and particle dispersion. With the aid of a sputter coater, a tiny piece of film is inserted into the carbon tape for examination.

7.2. Near-infrared (NIR) chemical imaging.

SEM research is accompanied by NIR chemical imaging. That's more objective in nature, so it helps evaluate opioid delivery over a wider surface range.

7.3. X-ray diffraction and Raman spectroscopy.

The crystalline or amorphous form of unprocessed APIs and APIs integrated into films can be calculated using X-ray diffraction patterns and Raman spectra.

7.4. Thickness measurements.

A Vernier caliper micrometer is used to measure the thickness of each film at five different positions (the middle and four corners). The average standard deviation of five replicate determinations describes the results.

7.5. Tear resistance.

Plastic film or sheeting tear resistance is a complex property of its ultimate shatter resistance. The force used to initiate tearing is measured using a very low loading rate of 51 mm (2 in)/min. The tear resistance value in Newtons is the highest stress or force needed to tear the specimen (which is usually located at the start of tearing).

7.6. Palatability study.

This research is focused on the sense of taste. According to the specifications, all batches are given A, B, or C scores. A formulation is called average when it receives at least one A degree. When a formulation receives two A grades, it is considered good, and when it receives all three A grades, it is considered very good. A is for outstanding, B is for good, and C is for bad.

7.7. Swelling characteristic.

Film swelling tests are carried out using a simulated saliva solution. Each film sample is weighted and put in a stainless steel wire mesh that has been preweighed. In a plastic tub, the mesh holding the film sample is immersed in a 15mL medium. The weight of the film was measured at fixed intervals before it reached a steady weight.

7.8. Weight variation.

Five distinct regions are represented by one cm^2 sample. Each film strip's weight is measured, and the weight difference is determined.

7.9. Folding endurance.

The film's folding durability is measured by folding one film at the same location before it splits. The value of the folding resilience is measured by the number of times the film could be folded at the same position without splitting.

7.10. Transparency.

A basic UV spectrophotometer can be used to calculate the clarity of the films. Cut the film samples into rectangles and mount them on the spectrophotometer's internal side. At 600 nm, assess the transmittance of films.

7.11. Determination of moisture uptake.

Films are sliced to a specific form. The moisture uptake of the films is assessed by exposing them to a regulated relative humidity and temperature setting for one week. The absorption of moisture by the films is determined and estimated using a formula that results in a percent increase in weight.

[(Experimental weight- Original weight)/ Original weight] x 100 = percent rise in weight

7.12. Drug content determination.

Any official assay method defined for the individual API in any standard pharmacopeias is used to decide the drug material.

7.13. Content uniformity.

The quality uniformity is calculated by spectrophotometrically estimating the API content in individual films using 20 films. The content uniformity should be between 85 and 115 percent, with a relative standard deviation of no more than 6%.

7.14. Tensile strength.

The apparatus, which has two clamps, the upper one set and the lower one movable, defines the tensile strength. Between the two clamps, the film sample (0.5 x 3 cm) is clamped. The tearing and elongation forces are calculated.

7.15. Water vapor transmission rate.

Vials of equal diameter can be used as transmission cells in water vapor transmission speeds tests. The cells are carefully cleaned and dried in an oven. One gram of calcium chloride is applied to the cell, and the polymeric films (two cm^2 area) have adhered to the brim with an adhesive. The cells are measured precisely, and the starting weight is registered. After that, the films are kept in a desiccator with a saturated potassium chloride solution (80-90 percent RH). After 18, 36, 54, and 72 hours, the cells are removed and measured. The sum of water vapor transmitted and the rate at which water vapor is transmitted can be measured using the rise in weights.

7.16. Contact angle measurement.

A goniometer is used to determine the contact angle. Within 10 seconds, a drop of distilled water is dropped on the dry film's surface, and photographs are captured using a digital camera.

7.17. Surface pH of films.

Films are allowed to swell for 2 hours on the surface of an agar tray, which is made by dissolving 2 percent w/v agar in a warmed isotonic solution of desired qualities and pouring the solution into a petri dish until it gels at room temperature. A pH paper placed on the surface of the swollen film may be used to assess the surface pH.

7.18. In-vitro disintegration time.

The in-vitro disintegration period is measured visually in a glass dish of 10 mL purified water and 10 seconds of swirling. The disintegration time is the time it takes for the film to fragment or disintegrate.

7.19. In vitro dissolution study.

The drug release tests are carried out using a dissolution research apparatus authorized by the USP (Paddle method). The USP dissolution apparatus is held at a constant temperature of 37°C and stirred at a speed of 50 revolutions per minute. Each film is mounted on a clear glass slide. The slide is then soaked in 500 mL of phosphate buffer pH 6.8 in a vessel. At intervals of 2, 4, 6, 8, 10, the aliquots of one ml are removed and replaced with an equivalent amount of dissolution medium. Throughout the analysis, the sink conditions are preserved. The absorbance is measured using a specific analytical tool.

7.20. Evaluation of organoleptic properties.

The OS must have suitable organoleptic palatable properties because they are meant to disintegrate easily or remain in the oral cavity for longer periods. The substance should have

the requisite sweetness and taste characteristics appropriate to a wider population. Special controlled human taste panels are used for psychophysical assessment of the substance. For this, in vitro procedures involving taste receptors, specially built apparatus, and drug release using adapted pharmacopoeial methods are being used. This in-vitro flavor evaluation equipment and methodologies are ideal for high-throughput taste testing of oral pharmaceutical formulations.

7.21. Packaging.

To protect the quick dissolving dosage types, expensive packaging, specific handling, and special care are needed during manufacturing and storage. Single packaging is mandatory. The most popular packaging material is an aluminum pouch. The Rapid card a proprietary and patented packaging system developed by APR-Labtec, especially for rapid films, is a proprietary and patented packaging system developed by APR-Labtec. Each side of the Rapid card contains three films and is the same size as a credit card. Per dosage may be taken separately.

The chosen material must meet the following requirements: it must not react with the substance. It has to keep the planning protected from the elements. It must be approved by the Food and Drug Administration (FDA). It must be impenetrable to tampering. It must not be harmful.

7.22. Packaging materials.

7.22.1. Foil, paper, or plastic pouches.

The lightweight pouch has a high level of tamper resistance as well as environmental security. During the product filling process, a compact pouch is created using vertical or horizontal shaping, filling, or sealing machinery. Single pouches or metal pouches may be used.

7.22.2. Single pouch and aluminum pouch.

The use of two structures helps one side to be transparent while the other uses cost-effective foil lamination. A single-dose pouch protects both the medication and the dosage. The most popular kind of pouch is aluminum.

7.22.3. Blister card with multiple units.

Heat softens a thermoplastic resin layer, then vacuum-drawn into a contoured mold to create a blister. The cavity is built to keep moisture out of the dosage form. The substance is filled into the semi-rigid blister that has already been formed, and the heat-sealable backing material is used to close it.

7.22.4. Barrier films.

Since certain drug formulations are highly sensitive to moisture, high barrier films are necessary. Moisture safety can be achieved using various materials, including polychlorotrifluoroethylene film and polypropylene. In certain circumstances, polypropylene would not stress break. It functions well as a gas and vapor shield. However, the lack of clarification is a downside.

8. Various Technologies Used in The Formulation of Fast Dissolving Oral Thin Films

BioProgress has developed platform technologies like Soluleaves™, XGEL™, WaferTab™ for formulating fast dissolving oral thin films.

8.1. Soluleaves™.

8.1.1. Features of Soluleaves ™.

a) A vegetable-based polymer film that carries low levels of active ingredients and flavoring
b) Fast dissolution in the mouth
c) Enhanced taste masking
d) Enhanced convenience, portability, and discreet format
e) Sugar-free variant suitable for diabetics
f) Aqueous based and solvent-free
g) Application in a range of vitamins, flavorings, and APIs
h) The Soluleaves™ system is patented

8.1.2. Foamburst™.

This is a Soluleaves^{TM} version in which an inert gas is injected into the film during creation. This produces a honeycombed film that melts quickly and provides a new mouth feel.

8.1.3. Xgel™.

The XGEL^{TM} film systems may encapsulate any oral dosage form and can be dissolved in cold or hot water. XGEL^{TM} film is made up of a variety of water-soluble polymers that have been precisely tailored for the application. All of the XGEL^{TM} ingredients are well known and generally regarded as safe (GRAS).

8.1.4. WaferTab™.

The WaferTab™ filmstrip can be flavored for additionally improved taste masking. The API is precisely dosed and integrated into the body of a pre-manufactured XGEL™ film, thus preventing exposure to unnecessary heat and moisture. Increasing the product's stability is a possibility. Since this WaferTabTM method allows numerous films with various actives to bond, it opens up many options for unique product design. WaferTab™ can be prepared in various shapes and sizes and is an ideal method for delivery of medicines which require a fast release or for use by patients who have difficulty swallowing.

9. Conclusions

Many pharmaceutical firms are moving away from tablets and fast-acting oral thin films. Films combine the benefits of tablets (precise dose, ease of application) and liquid dosage formulations (easy swallowing, rapid bioavailability). OTFs are a new emerging revolutionary drug distribution device that is critical in emergency cases where urgent intervention is required and that allows children, the elderly, and the general public to take their drugs discreetly whenever and wherever they are needed, filling a gap in the market. This technology establishes a solid foundation for developing patent-free inventions and extending

the patent lifecycle of existing ones. Quick dissolving oral thin films can be used with more than just buccal fast-dissolving processes; they can also be used for gastro-retentive and sublingual distribution systems. Incorporating incompatible active pharmaceutical ingredients in a single solution using multilayer films laminated together is one of the future applications. In between the incompatible active pharmaceutical ingredients, an inactive film sheet may be added to separate them. Thin films containing active pharmaceutical ingredients with high transmucosal flux concentrations can be incorporated into buccal or sublingual regions to dissolve slowly. Drugs that have been coated with controlled release polymers can also be used. This technology, though developed in the 1970s is being explored in-depth, and there is plenty of room for further studies in this area.

Funding

This research received no external funding.

Acknowledgments

This review has no acknowledgment.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Pandey, K.U.; Joshi, A.; Dalvi, S.V. Evaluating the efficacy of different curcumin polymorphs in transdermal drug delivery. *Journal of Pharmaceutical Investigation* **2021**, *51*, 75-78, https://doi.org/10.1007/s40005-020-00496-7.
2. Alaei, S.; Omidian, H. Mucoadhesion and Mechanical Assessment of Oral Films. *European Journal of Pharmaceutical Sciences* **2021**, *159*, https://doi.org/10.1016/j.ejps.2021.105727.
3. Damian, F.; Harati, M.; Schwartzenhauer, J.; Van Cauwenberghe, O.; Wettig, S.D. Challenges of Dissolution Methods Development for Soft Gelatin Capsules. *Pharmaceutics* **2021**, *13*, https://doi.org/10.3390/pharmaceutics13020214.
4. Özakar, R.S.; Özakar, E. Current Overview of Oral Thin Films. *Turkish Journal of Pharmaceutical Sciences* **2021**, *18*, https://doi.org/10.4274/tjps.galenos.2020.76390.
5. Drumond, N.; Stegemann, S. Better Medicines for Older Patients: Considerations between Patient Characteristics and Solid Oral Dosage Form Designs to Improve Swallowing Experience. *Pharmaceutics* **2021**, *13*, https://doi.org/10.3390/pharmaceutics13010032.
6. Dwivedi, K.P.; Gupta, A.; Pandey, S.; Singh, A. Fast dissolving drug delivery system: an overview on novel drug delivery system. *International Journal of Modern Pharmaceutical Research* **2021**, *5*, 19-32.
7. Patoliya, N.; Joshi, B.; Upadhyay, U. Future Prospect of Oral Disintegration drug Delivery system: A Review. *Research Journal of Pharmaceutical Dosage Forms and Technology* **2021,** *13*, 66-71.
8. Shaikh, S.S.; Barrawaz, A. Quality by Design Approach in the Formulation of Glibenclamide Mucoadhesive Buccal Films. *Analytical Chemistry Letters* **2021**, *11*, 497-511, https://doi.org/10.1080/22297928.2021.1938217.
9. Vihar, B.; Rozanc, J.; Krajnc, B.; Gradisnik, L.; Milojevic, M.; Cinc Curic, L.; Maver, U. Investigating the Viability of Epithelial Cells on Polymer Based Thin-Films. *Polymers* **2021,** *13*, https://doi.org/10.3390/polym13142311.
10. Radicioni, M.; Caverzasio, C.; Rovati, S.; Giori, A.M.; Cupone, I.; Marra, F.; Mautone, G. Comparative Bioavailability Study of a New Vitamin D3 Orodispersible Film Versus a Marketed Oral Solution in Healthy Volunteers. *Clinical drug investigation* **2022**, 1-11, https://doi.org/10.1007/s40261-021-01113-7.
11. Kagdi, R.; Le, K.; Doucet, D.; Ludlow, J.; Rinella Jr, J.V. Determination of holdup volume and transient contact compatibility of closed system transfer devices for a reconstituted lyophilized drug product. *Journal of Pharmaceutical Sciences* **2020**, *109*, 3504-3511, https://doi.org/10.1016/j.xphs.2020.07.031.
12. Vargason, A.M.; Anselmo, A.C.; Mitragotri, S. The evolution of commercial drug delivery technologies. *Nature Biomedical Engineering* **2021**, *5*, 951-967, https://doi.org/10.1038/s41551-021-00698-w.

13. He, M.; Zhu, L.; Yang, N.; Li, H.; Yang, Q. Recent advances of oral film as platform for drug delivery. *International Journal of Pharmaceutics* **2021**, *604*, https://doi.org/10.1016/j.ijpharm.2021.120759.
14. Mushtaque, M.; Muhammad, I.N.; Hassan, S.M.; Ali, A.; Masood, R. Development and pharmaceutical evaluation of oral fast dissolving thin film of escitalopram: A patient friendly dosage form. *Pakistan journal of pharmaceutical sciences* **2020** *1*, 183-189, http://dx.doi.org/10.36721/PJPS.2020.33.1.REG.183-189.1.
15. Chow, E.P.; Maddaford, K.; Hocking, J.S.; Bradshaw, C.S.; Wigan, R.; Chen, M.Y.; Howden, B.P.; Williamson, D.A.; Fairley, C.K. An open-label, parallel-group, randomised controlled trial of antiseptic mouthwash versus antibiotics for oropharyngeal gonorrhoea treatment (OMEGA2). *Scientific reports* **2020**, *10*, 1-7, https://doi.org/10.1038/s41598-020-76184-1.
16. Panraksa, P.; Qi, S.; Udomsom, S.; Tipduangta, P.; Rachtanapun, P.; Jantanasakulwong, K.; Jantrawut, P. Characterization of hydrophilic polymers as a syringe extrusion 3D printing material for orodispersible film. *Polymers* **2021** *13*, https://doi.org/10.3390/polym13203454.
17. Kshirsagar, T.; Jaiswal, N.; Chavan, G.; Zambre, K.; Ramkrushna, S.; Dinesh, D. Formulation & evaluation of fast dissolving oral film. *World Journal of Pharmaceutical Research* **2021**, *10*, 503-561, https://doi.org/10.20959/wjpr20219-21096.
18. Araujo, V. H. S.; Delello Di Filippo, L.; Duarte, J. L.; Spósito, L., Camargo, B. A. F. D.; da Silva, P. B.; Chorilli, M. Exploiting solid lipid nanoparticles and nanostructured lipid carriers for drug delivery against cutaneous fungal infections. *Critical reviews in microbiology* **2021**, *47*, 79-90, https://doi.org/10.1080/1040841X.2020.1843399.
19. Reddy Dumpa, N.; Bandari, S.; Repka, M.A. Novel gastroretentive floating pulsatile drug delivery system produced via hot-melt extrusion and fused deposition modeling 3D printing. *Pharmaceutics* **2020**, *12*, https://doi.org/10.3390/pharmaceutics12010052.
20. Vo, A. Q.; Zhang, J.; Nyavanandi, D.; Bandari, S.; Repka, M.A. Hot melt extrusion paired fused deposition modeling 3D printing to develop hydroxypropyl cellulose based floating tablets of cinnarizine. *Carbohydrate Polymers* **2020**, *246*, https://doi.org/10.1016/j.carbpol.2020.116519.
21. Özakar, R. S.; Özakar, E. Current overview of oral thin films. *Turkish Journal of Pharmaceutical Sciences* **2021**, *18*, 111, https://doi.org/10.4274/tjps.galenos.2020.76390.
22. Cascone, S.; Lamberti, G. Hydrogel-based commercial products for biomedical applications: A review. *International journal of pharmaceutics* **2020**, *573*, https://doi.org/10.1016/j.ijpharm.2019.118803.
23. Shestakov, Y. Development of robust SDKs for REST APIs in PHP: how to effectively develop, maintain and release REST API SDKs. Bachelor's thesis. Tampere University of Applied Sciences. January **2020**.
24. Baraldi, L.; Fornasari, L.; Bassanetti, I.; Amadei, F.; Bacchi, A.; Marchiò, L. Salification Controls the In-Vitro Release of Theophylline. *Crystals* **2022**, *12*, 201, https://doi.org/10.3390/cryst12020201.