Chapter

Thin Films: A Promising Approach for Drug Delivery System

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Abstract

The prime goal of drug delivery through drug carrier system to the specific target site at the suitable concentration for therapeutic action. Recently thin films are acquiring attention as drug carrier and various scientists are working on the formulation and development of thin films as a novel drug delivery system. Because of its capacity to safely load medications and release them in a regulated manner, thin films have attracted increasing interest in the field of drug delivery, which improves drug efficacy. They are more patient compliance and alternative to oral drug delivery employing self-application, prolonged action and easily terminate if drug toxicity is produced. Oral, buccal, sublingual, ocular, and transdermal routes have all been employed to deliver this delivery mechanism for both systemic and local effects. The development of thin films comprises of various methods with keeping in mind the anatomical and physiological constraints, physicochemical properties and types of drug substance and use of various polymers (matrix, hydrophilic and hydrophobic) as well as the characterisation methods with recent trends.

Keywords: film, prolonged action, film formation polymers, self-administration, local and systemic effect

1. Introduction

Biotechnological developments in the field of biomedical science have become more widely publicised in recent years, as the relevance of life extension and quality of life has become more widely recognised. Drug delivery system research, in particular, has been identified as one of the most challenging problems in biomedical science. In general, drug delivery system research focuses on keeping drug concentrations in the blood at a minimum and avoiding drug toxicity in vivo [1]. Thin films, in general, are ideal for targeting sensitive regions that tablets or liquid formulations may not be able to reach. Thin films have been shown to increase pharmaceutical action onset, dose frequency reduction, and treatment efficacy. Consequently, thin films may be beneficial in reducing excessive proteolytic enzyme metabolism and eliminating pharmaceutical side effects [2].

Thin films have demonstrated their ability to improve medication action onset, reduce dose frequency, and improve treatment efficacy. Thin films may also be useful

for decreasing excessive metabolism induced by proteolytic enzymes and removing the negative effects of medicine [3].

Penetration enhancers are substances that temporarily lessen the skin's impermeability, making it easier to absorb penetrant through the skin. These materials should be pharmacologically inert, non-toxic, non-irritating, non-allergenic, and compatible with the drug and excipients, odourless, tasteless, colourless, and inexpensive, as well as having good solvent properties. The enhancer must not provoke a loss of physiological fluids, ions, or other endogenous elements, and the skin should quickly regain its barrier properties after it has been removed [4]. Chemical penetration enhancers boost skin permeability by reversibly eroding or changing the physicochemical makeup of the stratum corneum to reduce diffusional resistance. Most chemical penetration enhancers irritate the skin, which is one of their drawbacks [5]. It's unsurprising that agents that interrupt ordered lipid patterns, cellular membranes, and components also disrupt ordered lipid structures, cell membranes, and constituents. The clinical utility of numerous chemical permeation enhancers has been limited due to the toxicity related to them. In recent years, the FDA has looked into essential oils, terpenes, and polymeric enhancers, all of which are GRAS (Generally Recognised as Safe) [6].

Polysaccharides, proteins, peptides, polyesters, and other substances are examples of natural polymers. Because of their biocompatibility and processability, the first two kinds of endogenous polymers were widely explored in the DDS. Because polysaccharides and proteins are more similar to the extracellular matrix, natural polymer-based medicament carriers are less intrusive. Furthermore, the polymers' backbones are plentiful in a variety of easy-to-change groups, such as amino groups, carboxyl groups, hydroxyl groups, and so on, allowing them to be easily modified [7]. Finally, as life science research developed, more specific connections between native polymers and organs or cells were uncovered. Natural polymers have been demonstrated to have a stronger affinity for cell receptors and to regulate cellular processes including adhesion, division, and migration, implying that they could be exploited to create more targeted and efficient high-efficiency applications [8]. Furthermore, their breakdown behaviour in the presence of enzymes in vivo ensures their potential to develop stimuli-responsive delivery in local locations.

The main objective of thin films delivers drugs topically, where they are absorbed by the skin and into the bloodstream. They provide consistent delivery of small amounts of a drug into the bloodstream over a long period. The duration of wear time and the amount of drug delivered is different from film to film.

2. Advantages and disadvantages over conventional dosage form

2.1 Advantages

First, there are biological advantages to delivering drugs through the skin:

1. Transdermal distribution avoids the stomach environment, where the medicine may decay and become ineffective, or where it may cause the patient to experience unpleasant gastrointestinal symptoms [9].

2. The first-pass effect, in which active medication molecules are transformed to inactive molecules or even molecules that cause side effects, is avoided with transdermal distribution [10].

3. Transdermal medication administration ensures consistent plasma concentrations. When a patch is applied for 24 hours or even 7 days, the plasma levels remain consistent once a steady state is attained since the rate of drug delivery from the patch is constant. When a medicine is given four times a day, or even once a day, the drug levels rise immediately after administration and then gradually fall until the following administration, resulting in peaks and troughs throughout treatment [10].

4. TDDS, in contrast to limited controlled release via oral and intravenous routes, provides a continuous infusion of the drug over an extended period, making it ideal for drugs with a short biological half-life that requires frequent dosing, resulting in increased patient compliance and decreased inter and intra-patient variability [11].

5. It is possible to avoid therapeutic failure or the side effects that are usually linked with intermittent dosage for chronic diseases [12].

6. When necessary, self-administration and removal are feasible [13].

7. This non-invasive and safe parenteral route of drug delivery helps take away the pain and inconvenience of injections [13].

2.2 Other advantages to delivering drugs through the skin

1. Transdermal medication delivery devices, particularly simple thin films, are simple to use and non-invasive, which patients prefer [14].

2. Thin films can improve compliance and lower medical expenditures because they are simple to use. Many studies suggest that increasing pharmacological compliance lowers a patient's overall healthcare costs. Furthermore, studies have shown that prescribing thin films improves patient compliance and lowers healthcare expenses [15].

3. Medical waste can be reduced by using a transdermal delivery device instead of a needle, lowering healthcare expenditures once again.

2.3 Disadvantages

1. Many drugs especially drugs with hydrophilic structures that permeate the skin too slowly may not achieve a therapeutic level.

2. The drug, the adhesive or other excipients in the thin film formulation can cause erythema, itching, and local oedema.

3. The barrier function of the skin changes from one site to another on the same person, from person to person and also with age.

4. Daily dose of more than 10 mg is not possible.

5. Local irritation is the major problem.

6. Drugs with a long half-life cannot be formulated in the thin film.

7. It May not be Economical.

8. Barrier function changes from person to person and within the same person.

9. Heat, cold, sweating (Perspective) and showering prevent the thin film from sticking to the surface of the skin for more than one day. A new thin-film has to be applied daily.

10. In case of any medical emergency, the thin film is not a good choice.

3. Routes of thin films administration

3.1 Oral route

The oral route has traditionally been chosen over other existing administrative methods due to its ease of administration, patient compliance, and possible formulation flexibility. The buccal area (buccal mucosa) of the oral cavity provides an appealing channel for medication delivery for both local and systemic activities. Buccal mucosa possesses morphological and physiological properties that make it a good drug delivery route, including the presence of smooth muscles with high vascular perfusion, high accessibility, minimal enzymatic activity, and escape of hepatic first-pass metabolism. However, the formulation's transit duration at an application location is limited by the constant salivary flush in the mouth cavity. More study into the use of bioadhesive polymers to prolong the residence time (RT) of formulations in living tissue has resulted as a result of this [16]. Drug delivery through to the buccal mucosa has been accomplished with tablets, lozenges, chewing gums, sprays, films, patches, hydrogels, pastes, ointments, solutions, microspheres, and other dosage forms, but buccal films have been reported to be the most favourable and successful strategy for delivering through the epithelium with greater patient compliance [17].

The microenvironment of the mucosa controls medication disintegration (release) and penetration through the mucosa. The environment of the mucosa can be modified or transformed with the help of well-designed mucoadhesive drug delivery devices [17]. These systems are designed and formulated with mucoadhesive polymers, which are generally of high molecular weight and high viscosity grades with improved flexibility and optimal chain length. A variety of mucoadhesive polymers have also been used to study buccal drug delivery. Buccal films are superior to oral gels and buccal tablets among mucoadhesive drug delivery systems due to their long residence time, more flexibility in covering the buccal mucosa, and improved comfort [18]. The major goal of this study was to create a buccal mucoadhesive patch that would maintain a stable miconazole level in the mouth for lengthy periods. The created patch's performance will be compared to that of a commercial oral gel. In addition, the effect of ageing on the produced patches' mucoadhesive function will be examined.

The oral route, which includes buccal mucosa, is the most suitable for both local and systemic drug delivery among the different locations accessible for mucoadhesive drug delivery. The created buccal mucosal membrane by Jacob S et al., 2021 presents an appealing drug-delivery channel to boost both systemic and local therapy. The advantages and disadvantages of buccal drug delivery, anatomical and physiological

characteristics of the oral mucosa and several in vitro techniques often employed for assessing buccal drug-delivery systems are all discussed in this paper. The importance of mucoadhesive polymers, penetration enhancers, and enzyme inhibitors in overcoming formulation problems, including the salivary refurbishment cycle, masticatory effect, and limited absorption area, is discussed. Because of their flexibility, convenience, lightness, acceptability, ability to endure mechanical stress, and specific size, biocompatible mucoadhesive films and patches are preferred dosage forms for buccal administration. The methods of preparation, the scaling-up process, and the manufacturing of buccal films are discussed [19].

Furthermore, Semalty et al. develop mucoadhesive buccal films of enalapril maleate to increase therapeutic efficacy, patient compliance, and bioavailability. Using the solvent casting technique, five formulations of mucoadhesive drug delivery systems of enalapril maleate were created as buccal films in this study. Mucoadhesive polymers employed were sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, and polyvinyl pyrrolidone K-90. In permeation tests, films showed controlled release for more than 10 hours. The films containing 20 mg of enalapril maleate in sodium carboxymethylcellulose 2% w/v and hydroxyethylcellulose 2% w/v showed good swelling, a convenient residence time, and promising controlled drug release, and thus can be chosen for the development of buccal films for effective therapeutic uses [17].

3.2 Ocular route

The thin layer provides a variety of functions as the interface between the ocular surface and the external environment. It generates a refracting thin coating on the corneal surface that smooth's out the uneven topography. It maintains a somewhat constant extracellular environment for corneal and conjunctival epithelial cells in terms of pH, oxygen and carbon dioxide levels, nutrition, and growth factor concentrations. Microorganisms, which are also combated by a complex and powerful antibacterial system, are diluted and washed away by tears. The tear film changes its composition in response to physiological events. The human tear film appears to be quite stable and attached to the cornea while the eyes are maintained open, taking up to 60 seconds to disclose the initial break. When a contact lens is implanted, a stable tear film is not maintained throughout the lens, and the surface dries up between blinks. The tear film on the surface of a contact lens begins to break up in 4–6 seconds (hard) or 7–9 seconds (soft) when a human blinks once every 10 seconds on average. The single most critical element in deposit formation and long-term discomfort during contact lens usage is lens drying. Several theories have been presented to explain this phenomenon. A thin film containing surface-active molecules like those found in tears should not rupture as quickly from a curved surface, according to physical chemistry. Experiments with lenses in the lab have shown that certain lens surfaces may hold a water coating for up to 2 minutes. On-eye surface dryness is caused by many reasons. With a stiff lens, drainage is unavoidable due to the tear meniscus, which is evident around the lens periphery. With the lens on the eye, the structured layers of the tear film are unable to form up as they do on the cornea. Another explanation is that the lipid layer is thin or disturbed, leaving the tear film vulnerable to evaporation. Early tear components binding to lenses might also impair wettability [20].

It has various advantages for ocular distribution, including sanitation, ease of eye drop formulation, less irritation, increased precorneal residence duration, and improved ocular bioavailability of medications that are insoluble in tear fluid. In 2015,

Mahajan HS and Deshmukh SR investigated the use of xyloglucan, a polysaccharide polymer, as a new film-forming agent for ciprofloxacin ocular administration. Ciprofloxacin ocular films were made utilising xyloglucan and the solvent casting process (2%). The formulas were made following the unusual transport release mechanism. The formulation is safe for the ocular mucosa, according to an ocular irritancy study. As a result, this research proposes that xyloglucan could be used as a film-forming polymer for ciprofloxacin ocular administration [21].

3.3 Transdermal route

Topically given pharmaceuticals in the form of patches that, when placed to the skin distributes the drug through the skin at a predetermined and controlled pace are referred to as transdermal drug delivery systems. Transdermal patches distribute drugs via the skin in a controlled and predefined manner, resulting in increased therapeutic efficacy and fewer side effects. The medications must be able to permeate the skin and reach the target site to be effective in a transdermal drug delivery system. When compared to the oral route, TDDS improves patient compliance and reduces load [6].

Transdermal delivery of drugs through the skin to the systemic circulation is a useful methodology of administration for a variety of clinical indications. Transdermal delivery systems are available for scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, nicotine for cessation of smoking, oestradiol (alone or in combination with levonorgestrel or norethisterone) for hormone replacement, and testosterone for hypogonadism [22].

Some of the possible benefits of transdermal drug delivery include controlled absorption, more consistent plasma levels, increased bioavailability, decreased adverse effects, painless and uncomplicated application, and the flexibility of discontinuing drug administration by simply removing the patch from the skin. Padula et al. reported a novel drug delivery system consisting of a water-based, vapour permeable membrane for cutaneous and/or transdermal distribution. The goal of this study was to control the administration of the model drug lidocaine hydrochloride through rabbit ear skin using a transdermal film. On lidocaine transport over the skin, the effects of drug loading, film-forming polymer type and content, adhesive and plasticiser were studied [23]. Aside from that, Ammar HO et al. (2013) developed and tested a transdermal ketorolac film-forming polymeric solution for pain treatment employing Eudragits® RLPO, RSPO, and E100, as well as polyvinyl pyrrolidone K30 dissolved in ethanol as film-forming solutions. An improved transdermal ketorolac formulation has shown a significant potential to provide a rapid and enhanced analgesic impact, which is a critical requirement in pain treatment [24].

4. Film formation polymers

The FFS is built on a foundation of polymers, and a range of polymers are available for this purpose. These polymers can be employed alone or in conjunction with other film-forming polymers to get the necessary film characteristics at skin temperature, these polymers should produce a clear flexible film. The **Table 1** shows a list of polymers, along with their molecular weights and properties [15].

Polymer	Properties	Use	References
Hydroxypropyl methylcellulose (HPMC)	Moderate tensile strength, moisture and oxygen barrier characteristics, elasticity, transparency, and oil and fat resistance.	HPMC is used as a raw material for coatings with moderate strength and elasticity in Film, transparency.	[25, 26]
Hydroxypropyl cellulose (HPC)	HPC used for artificial tears, emulsion stabiliser, Binder, thicke ner, white to slightly yellow tinted, odourless, inert, and tasteless powder Absolute ethanol, methanol, isopropyl alcohol, and propylene glycol are all polar organic solvents that are soluble in both cold and hot temperatures. Mucoadhesive characteristics are moderate.	Used as an excipient, and topical ophthalmic protectant and lubricant and also used in ophthalmic films.	[27, 28]
Carboxymethyl cellulose (CMC)	Anionic, water-soluble cellulose derivative, rapid hydration, High swelling strength, Good bioadhesive properties.	Used as a flocculant, chelating agent, surfactant, thickening agent, water-retaining agent, sizing agent, and film-forming material, among other things.	[29]
Polyvinyl pyrrolidone	Solubility across a wide range, Non-ionic substances, Susceptibility to swelling, Used as a mucoadhesion enhancer as a co-adjuvant.	Food additive, stabilizer, in paints and also having film-forming property.	[30, 31]
Poly ethylene oxide	For the polymer that is not ionic, Mucoadhesion is high when the molecular weight is high.	Used to deliver drugs in the transdermal and transmucosal system.	[32, 33]
Pectin	Non-ionic, high swelling characteristics, a wide range of solubility To increase mucoadhesion, it's used as a co-adjuvant.	Food, beverages, pharmaceuticals, drug and vitamin capsules, photographic films, thin-film, and cosmetics all employ it as a gelling agent.	[34, 35]
Chitosan	Odourless white or creamy powder or flakes After chitin has been partially deacetylated, Biodegradable and biocompatible Water is sparingly soluble; ethanol (95 per cent), various organic solvents, and neutral or alkali solutions with pH more than 6.5 are practically insoluble.	Chitosan has the potential to be employed as a medication carrier, a tablet excipient, a Film Forming agent, and a delivery platform for parenteral formulations, among other applications.	[36, 37]
Sodium alginate	It appears as a white or buff powder with no odour or taste. Purified carbohydrate product obtained by dilute alkali extraction from brown seaweed, is insoluble in other organic solvents and acids. Anionic has a high mucoadhesive capacity, is Non-allergenic, biodegradable, and safe In water, rapid swelling and dissolution.	Stabilisers in emulsions, suspending agents, tablet binders, and tablet disintegrants are all examples of film-forming properties.	[36, 38]
Carrageenan	Lota, Kappa, and Lambda are three structural kinds with different	Used in the food technology and pharmaceutical industry for their	[39, 40]

Polymer	Properties	Use	References
	solubility and rheology. All three kinds of sodium are soluble in both cold and hot water. pH 6 to 10 provides the optimum solution stability. Mucoadhesive characteristics are moderate.	gelling, thickening, stabilising and also having film-forming properties.	
Gelatin	A powder that ranges in colour from light amber to pale yellow. The molecular weight ranges from 15,000 to 250,000. Glycerin, acid, alkali, and hot water are all soluble in it. 9–11 per cent (w/w) moisture content.	Giving flexibility, stability and prolonged life span for the thin film.	[41, 42]
Poly (vinyl alcohol) (PVA)	Molecular weight 20,000–200,000, white to cream-coloured granular powder Synthetic polymer that is water-soluble, Polymer that is not ionic, Mucoadhesive characteristics that are moderate.	As buccal films, nanotechnology, hydrogels, and transdermal patches.	[43, 44]

Table 1.
Film formation polymers.

5. Category of thin films

Thin film is not a new preparation; it was initially launched in the late 1970 to help people take tablets and capsules that were difficult to swallow. The oral film, oral thin film, orodispersible film, oral soluble film, wafer, oral strip, buccal film, mucoadhesive film, transmucosal film, ocular film, and transdermal and topical film are some of the names given to thin films [2].

5.1 Oral film (oral thin film)

Oral films are composite polymeric matrices that may be employed as drug delivery platforms effectively. To generate elegant drug delivery platforms, these polymeric matrices can be made up of a variety of components, however, hydrophilic polymers are frequently in the centre. The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) both refer to a thin film that rapidly dissolves in the oral cavity as orodispersible film. Oral films originated as unique breath-freshening formulations, but they swiftly evolved to satisfy several commercial needs, including a convenient and easy-to-swallow medicine delivery method [15].

5.1.1 Orodispersible film/oral soluble films

Because of its simplicity of administration, non-invasiveness, flexibility, patient compliance, and acceptance, the oral route of medication administration is the most popular. When put on the tongue, orally disintegrating films quickly hydrate via soaked saliva after the breakup and/or dissolution, liberating the active pharmacological substance from the dosage form. Orodispersible films are a type of formulation

that is often made with hydrophilic polymers and allows for fast disintegration when exposed to saliva. Oral disintegrating tablets and oral disintegrating films are two typical oral disintegrating medicine administration strategies. These systems were developed in the late 1970s as an alternative to standard dosage forms such as quick-dissolving tablets and capsules for elderly and paediatric patients who had difficulty swallowing traditional dosage forms [45].

Orodispersible films, on the other hand, are flexible while remaining resistant to mechanical stresses. While lyophilization is a standard method for creating oral disintegrating tablets, orodispersible films are made using a technology similar to that used to make transdermal patches, which is less costly than lyophilization. Orodispersible films are preferable to liquid dosage forms such as drops or syrups because they allow for precise dosage. A quick beginning of effect might be obtained since the medication is delivered into the oral cavity in seconds. Some medications can bypass first-pass metabolism if they are absorbed through the oral mucosa, which may boost bioavailability. To ensure a strong production and packaging process as well as ease of handling and administration, an ideal orally disintegrating film must be thin and flexible, yet sturdy. The films must be transportable, non-sticky, and maintain a level shape without rolling up. They should have a nice taste and a comfortable tongue feel. The time it takes for something to disintegrate should be as quick as feasible. Because of the inverse link between mechanical qualities and disintegration time, meeting all of these parameters is difficult [46].

5.1.2 Wafers

Wafers are paper-thin polymer sheets that are used to transport pharmaceuticals. The novel dosage form is taken orally and does not need the use of water or swallowing. The wafer dissolves fast in the mouth, allowing the active substance to be taken into the bloodstream through the oral mucosa. The active component escapes the liver's first-pass action once absorbed by the oral mucosa, improving bioavailability. Based on the chosen wafer type, the active substance delivery may also be delayed. In this situation, it is absorbed through the gastrointestinal tract after ingestion [47].

Wafers that have been lyophilized and positioned on the patient's tongue grip saliva fast and dissolve within seconds, releasing the medication. Developing a dose form that improves patient confidence and acquiescence, principally intended for oral/buccal drug delivery systems, is becoming increasingly difficult. Buccal wafers are preferred over other dosage forms because of their small dimensions, low dose, and thickness. For paediatric and geriatric patients, the lyophilized oral wafer medication delivery method offers a substitute for tablets, capsules, and liquid oral dosage forms. When compared to alternative dose forms, lyophilized wafers have a bigger surface area, ensuring improved patient compliance, particularly in geriatrics and paediatrics. A good buccal wafer ought to be flexible, elastic, and easy-going, as well as have good bioadhesive characteristics to stay in the mouth cavity for the specified amount of time [48].

5.1.3 Oral strip

The oral strip, a thin film made of hydrophilic polymers that liquefy quickly on the tongue or in the buccal cavity, is one such relatively recent dosage form [49]. Oral medication delivery has progressed from basic conventional tablets/capsules to

modified-release tablets/capsules to oral disintegrating tablets to wafer to the newest creation of oral strips due to research and development. Essentially, an oral strip is a postage-stamp-sized ultra-thin strip containing an active agent or active medicinal component as well as additional excipients. The simplicity of administration and portability of oral strips have led to a greater acceptance of this dose form among both paediatric and geriatric patients [50].

However, because the oral strip technology's derived devices were easily available in the marketplace in the type of breath-freshening strips, no additional determinations were required to re-instruct the general public on how to administer this dosage form. With the release and well-known usage of Listerine pocket strips, a novel unveiling in the mouthwash line, oral strip tools was already popular among the public in the early 2000s. This delivery mechanism can accommodate a wide range of compounds. Cough/cold cures (antitussives, expectorants), sore throat, erectile dysfunction medications, antihistaminics, antiasthmatics, gastrointestinal issues, nausea, pain, and CNS stimulants are just a few examples (e.g. antiparkinson disease). Caffeine strips, snoring aids, multivitamins, and sleeping aids are some of the other applications [51].

5.1.4 Buccal film

The buccal films are designed to deliver drugs to the mouth mucosa. This aim may be supplementary difficult to achieve than it appears, as increased mouth residence duration is far from the sole influencing factor. In the direction of circumventing inter and intra-individual inconsistency, the oral mucosa drug saturation ought to be taken into account, as well as one-way absorption. As a result, multilayer films have been coined as an innovative term for buccal films. The benefits of this medication delivery technology are substantial. Beyond patient acceptance, the oral cavity has many advantages for medication administration [15].

Because the buccal mucosa has a small surface area meant for application of the buccal delivery system, device dimensions and drug load are constrained. The real region for medication absorption is determined by the dosage form's size. For buccal distribution, a device with a surface area of 1–3 cm2 and a daily dosage of 25 mg or a lesser amount is preferable. Because meal ingestion and/or drinking may necessitate the removal of the delivery device, the maximum duration of buccal medication administration is roughly 4–6 hours. The more rapid turnover of the buccal mucosal epithelium (3–8 days) compared to the skin (30 days) may alter medication absorption by altering penetrability properties regularly [52].

5.1.5 Mucoadhesive film

Mucoadhesive films are retaining dosage formulae that deliver the medication into the biological substrate directly. Furthermore, as compared to lozenges and tablets, films ensure greater patient acquiescence owing to their small dimensions in addition to compact thickness. Some of these benefits, as well as others, are shared by mucoadhesive buccal films. In comparison to tablets, they have increased patient compliance in line with their modest size and thickness. Furthermore, because mucoadhesion entails addition to the buccal mucosa, films can be designed to have either a systemic or local effect. Numerous mucoadhesive buccal films have been developed to release drugs locally in the mouth cavity to treat fungal diseases such as oral candidiasis. The release can be focused on either one towards the buccal mucosa

or towards the oral cavity due to the adaptability of the production methods; in the latter instance, it can give controlled release via gastrointestinal (GI) tract administration. On the other hand, films that deliver the medicine to the buccal mucosa can be created. Using directing absorption through the venous system that drains from the cheek, films delivering medicine towards the buccal mucosa prevent the first-pass effect [53]. The majority of polymers utilised as mucoadhesives are hydrophilic polymers that expand and let for chain connections with the mucin molecules in the buccal mucosa [54]. Hydroxypropyl cellulose (HPC), hydroxypropylmethylcellulose (HPMC), hydroxyethylcellulose (HEC), sodium carboxymethyl cellulose (SCMC), poly(vinyl pyrrolidone) (PVP), and chitosan are examples of swellable polymers.

5.1.6 Transmucosal film

Oral transmucosal distribution, particularly buccal and sublingual delivery, has advanced well beyond the use of traditional dosage forms, with new techniques being developed regularly. These transmucosal drug delivery methods have several benefits above oral administration meant for systemic drug delivery, together with the ability to skip the first pass effect and avoid presystemic elimination inside the GI tract. The administration of medications to the oral cavity has gotten a lot of interest because of its high potential for patient compliance and unique physiological characteristics. The distribution of medications within the mouth mucosal cavity is divided into dual categories: local delivery and systemic administration by the buccal or sublingual mucosa. Another key physiological obstacle to oral transmucosal drug administration is drug permeability through the mouth (e.g. buccal/sublingual) mucosa. The thickness of the oral mucosa, as well as the makeup of the epithelium, varies depending on the location [55].

5.2 Ocular film

The prognosis for visual illnesses such as glaucoma, age-related macular degeneration, diabetic macular oedema, and retinal vascular occlusions has considerably improved because of recent improvements in pharmaceutical therapy. As a result of these advancements in pharmacological therapy, there is a lot of interest in less invasive delivery methods, which has resulted in significant progress in the field of ocular drug administration. Therapeutic substances are difficult to distribute due to the anatomy of the eye. Due to the blood-ocular barrier, which compartmentalises the eye, as well as the eyewall itself, the eye is resistant to substantial quantities of external chemicals (cornea and sclera). Pathogens are prevented from accessing ocular tissues by the blood-ocular barrier, which also inhibits systemic pharmacologic drugs from reaching potential ocular tissue targets [56].

Ocular film lengthens the contact period, allowing for a more controlled release, lowering administration frequency, enhancing patient compliance, and increasing therapeutic efficacy. The main goal of the ocular film is to improve the contact period between the film and the conjunctival tissue to create a long-lasting formulation suited for topical or systemic therapy [57].

5.3 Transdermal and topical film

A unique technique, the film-forming technology, can be employed as an alternative to traditional topical and transdermal formulations. It's a non-solid dose form that forms a film in situ, or after being applied to the skin or any other bodily surface.

These systems include the drug and film-forming excipients in a vehicle that, when it comes into contact with the skin, evaporates leaving a film of excipients and the drug behind. The produced film can be a solid polymeric substance that works as a matrix for drug release to the skin over time or a residual liquid film that is quickly absorbed in the stratum corneum [58, 59]. The purpose of medication administration through the skin is to treat skin illnesses on a topical level or to allow pharmaceuticals to enter the systemic circulation via transdermal absorption. The topical method provides a vast and diverse surface, as well as simplicity of application by self-administration, and is a viable option to both oral and hypodermic drug delivery [60, 61]. The rate and degree of medication absorption via the skin are influenced by skin physiology, drug physicochemical qualities, and delivery mechanism [62]. The avoidance of first-pass metabolism and other GI tract factors such as pH, stomach emptying time, and others are among the benefits of transdermal film. Deliveries that are consistent and managed over a lengthy period, Minimization of peaks and troughs in blood-drug concentrations to reduce adverse effects associated with systemic toxicity. Treatment of skin diseases such as psoriasis, eczema, and fungal infections, for example, requires direct access to the target or afflicted location. Dose cessation is simple in the case of any systemic or local adverse effects [63].

6. Methods of preparation

Solvent casting and hot melt extrusion are the two most common methods for making oral films. However, several new advancements and novel ways have developed in recent years. Semisolid casting and solid-dispersion extrusion are two versions of these industrial technologies of casting and extrusion that have been defined and utilised alone or in combination. **Figure 1** showing innovative manufacturing processes, such as rolling and printing, are also discussed.

6.1 Solvent evaporation

The most typical approach for preparing thin films utilising water-soluble excipients, polymers, and drugs that are dissolved in de-ionised water is solvent evaporation; as a result, a homogeneous mixture is formed by applying high shear forces generated by a shear processor. To get good quality films, the prepared solution is placed onto a Petri plate and the solvent is allowed to dry by exposing it to high temperatures. The film-forming polymer is normally immersed in a suitable solvent overnight in the solvent casting procedure. The type of API that must be included in the film determines the appropriate solvent based on essential physicochemical parameters of the API such as melting temperature, shear sensitivity, and polymorphic form. Before completing a formulation, the drug's compatibility with the solvent and other excipients is taken into account. Entrapment of air bubbles during formulation might affect the homogeneity of produced films. **Figures 2** and **3** indicating the deaeration of the mixture is therefore accomplished with the aid of a vacuum pump [45].

6.2 Semi-solid casting

When the film constituent is an acid-insoluble polymer, this approach is favoured. The water-soluble polymers are initially dissolved in water in this step. The resulting solution is mixed with an acid-insoluble polymer solution that has been prepared

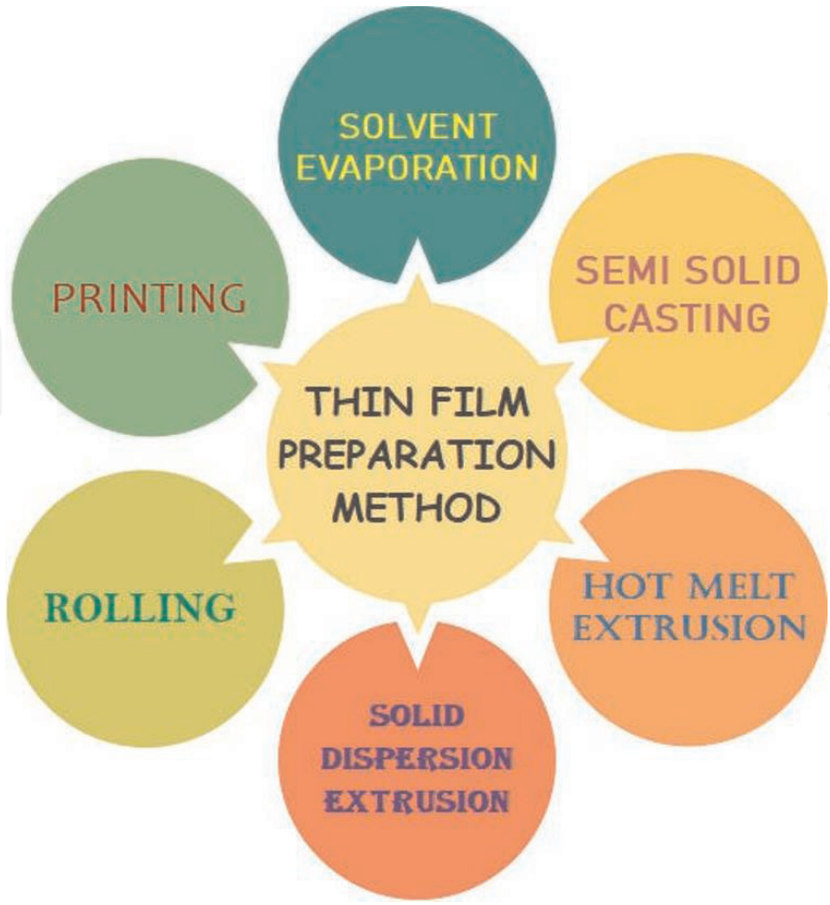

Figure 1.
Methods of preparation for thin films.

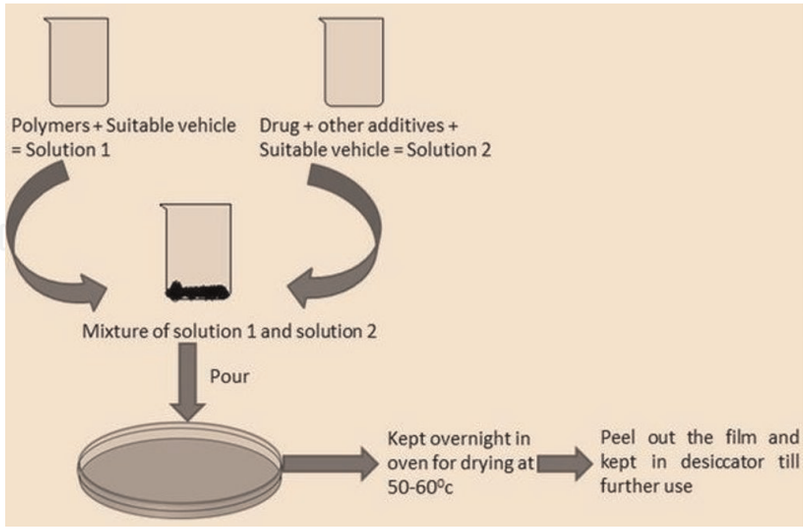

Figure 2.
Solvent evaporation method [64].

separately. Both solutions have been thoroughly combined. Following the mixing of the two solutions, a sufficient quantity of plasticiser is added to the final solution to get the gel's mass. Finally, using heat-controlled drums, the gel mass is cast onto the films or ribbons. The film thickness should be between 0.015 and 0.05 inches. The acid-insoluble polymer should be used at a 1:4 ratio with the film-forming polymer.

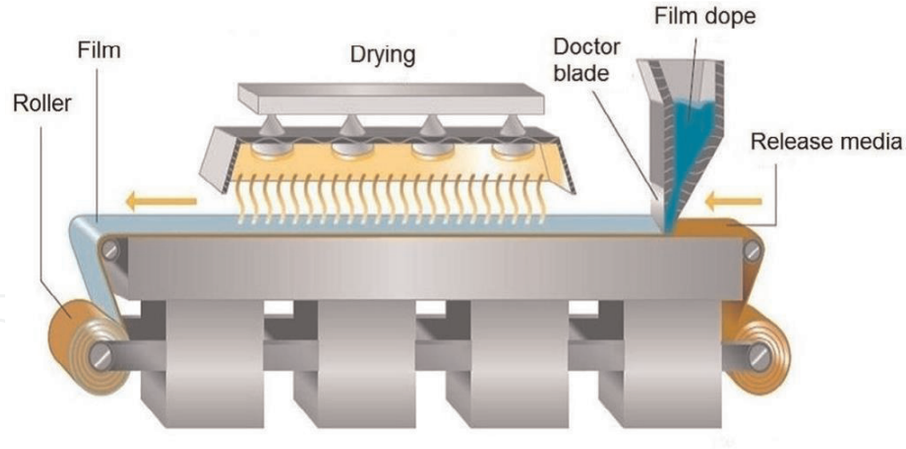

Figure 3.
Industrial machine for film formation by solvent evaporation [15].

Cellulose acetate phthalate and cellulose acetate butyrate are examples of acid-insoluble polymers [65].

6.3 Hot melt extrusion

Granules, prolonged-release tablets, transdermal and transmucosal drug delivery devices are all made with hot-melt extrusion shown in **Figure 4**. Rather than using the traditional solvent casting approach, this technique uses heating a polymer to shape it into a film. API and other components are combined in a dry state, then heated, and finally extruded out in a molten form in this procedure. There are no solvent systems involved in these operations. The film is cast from the molten mass that has resulted. The films are then cooled further before being cut to the proper size. Due to the utilisation of extremely high temperatures, this technique is not suited for thermolabile APIs. The casting and drying processes are crucial. Commercial-scale production necessitates the optimization of casting speed and drying time. Lower temperature and shorter residence time of the drug carrier mix, lack of organic solvents, continuous operation, little product waste, good control of operational parameters, and the ability to scale up are all features of this method [66].

6.4 Solid dispersion extrusion

The method entails incorporating a solid dispersion of the drug into a melted polymer solution to load the medication. To make a solid dispersion, the medication is dissolved in a suitable liquid solvent and then added to a melt of a suitable polymer that is attainable below 70°C without removing the liquid solvent. Finally, the dyes are used to form the solid dispersions into films [65].

6.5 Rolling

Water and a combination of water and alcohol are the most common solvents employed in this procedure. The active substance and other components are dissolved in a small amount of aqueous solvent using a high shear processor. Hydrocolloids that are water-soluble are dissolved in water to create a homogeneous viscous solution. The

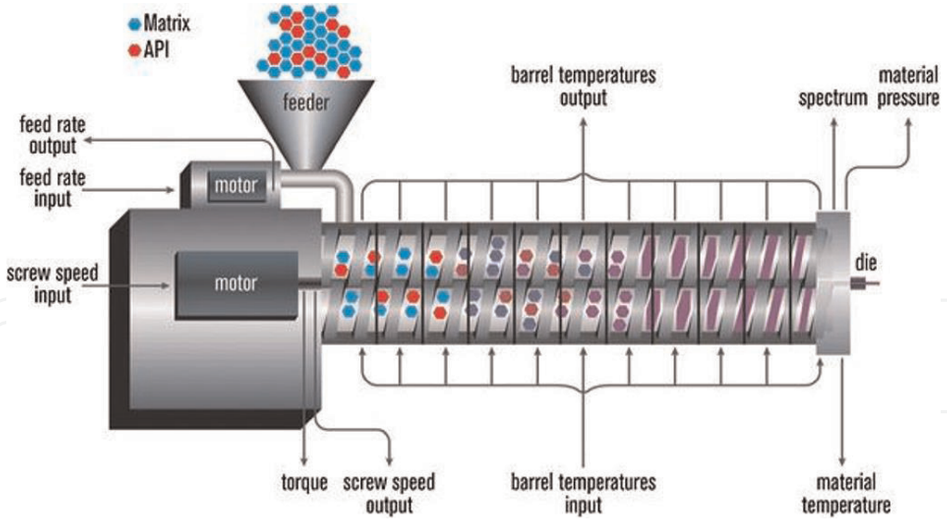

Figure 4.
Hot melt extrusion [67].

drug-containing solution or suspension is then rolled onto a carrier. After that, the film is cut into the proper shapes and sizes [68].

6.6 Printing

Polymeric thin films might be manufactured using novel technologies such as 3D printing. It might be a platform for developing the dose form that is most useful to the specific patient. Because of their versatility and cost-effectiveness, printing technologies are becoming increasingly popular. Printing technologies are extensively used in the pharmaceutical sector for identifying or labelling pharmaceutical dosage forms, especially to make the product more easily identifiable and to prevent counterfeit manufacture. However, this method has just lately been used to load drugs into medicinal dosage forms. The use of off-the-shelf consumer inkjet printers with drug-loaded inks to produce precisely dosed units of medicinal components is one example. Additionally, a hybrid of inkjet and flexographic technologies has been employed. Inkjet printing was utilised to print API on various substrates, while flexographic printing was used to cover the drug-loaded substrate with a thin polymeric coating [2].

In the all adopted method of preparation for thin films listed above like solvent evaporation, semisolid casting, hot-melt extrusion, solid dispersion extrusion, rolling and printing, the solvent evaporation method is more recommendable and mostly used. Evaporative systems provide passive and non-occlusive delivery of drugs. Therefore, this system is well tolerated and also demonstrates very low skin irritation rates. Compared to physical technologies they are having a simple working mechanism and more importantly they provide non-invasive drug delivery. Apart from that solvent evaporation method is more economical, reproducible and more efficient.

7. Characterisation aspects

Several attempts have been made to establish appropriate procedures for evaluating and characterisation of oral films, taking into account their unique properties. Certain essential criteria should be assessed for film quality control.

7.1 Surface morphology

Scanning Electron Microscopy (SEM) is used to examine the morphology of the films at various magnifications [69].

7.2 Thickness

Micrometre screw gauges or calibrated digital Vernier Callipers are used to determine the thickness of the film. The film thickness should be in the range of 5–200 μm. The thickness of the film should be measured at five distinct sites (four corners and one in the middle), and consistency in the thickness of the film is critical because it affects the accuracy of dosage distribution in the film [65].

7.3 Weight variation

The weight variation is usually calculated to guarantee that each film has the same quantity of a drug every time it is used. It's computed by weighing individual films and averaging the weights of a group of films. The individual weight of patches is deducted from the average weight of the film.

7.4 Elongation

The strain occurs when stress is given to a film ($2 \times 2\ cm^2$) sample, which causes it to stretch. Strain is the distortion of a strip before it breaks due to stress. The formula for calculating it is as follows-

$$\%Elongation = \frac{Increase\ in\ length\ of\ film}{Initail\ length\ of\ film} \times 100 \quad (1)$$

7.5 Tensile strength

The greatest stress applied to a point where the film specimen breaks are known as tensile strength. As shown in the equation below, it is computed by dividing the applied load at rupture by the cross-sectional area of the film.

$$Tensile\ strength = \frac{Load\ at\ failure}{Film\ thickness \times Film\ width} \times 100 \quad (2)$$

7.6 Tear resistance test

The complicated function of a film's final resistance to rupture is its tear resistance. The tear resistance value is the maximum force necessary to rip the film. The plastic industry is usually blamed for this test. The loading rate used is 2 in/min, which is intended to quantify the degree of force necessary to rip the film specimen. The highest amount of force required for tearing is usually observed around the tearing commencement, and this number is referred to as tear resistance value [70].

7.7 Young's modulus

Young's modulus, often known as elastic modulus, is a measure of a film's stiffness or elasticity. This reflects the films' resistance to deformation, which may be measured by graphing the stress–strain curve, where the slope denotes the modulus, i.e. the higher the slope, the higher the tensile modulus. The narrow slope, on the other hand, indicates a lower tensile modulus and deformation. Simply put, a film with higher tensile strength and greater Young's modulus values is rigid, brittle, and has little elongation. The Young's modulus may be measured with a texture analyser, with the slope acquired from the stress–strain curve [2]. Young's modulus is defined as the ratio of applied stress to strain in the elastic deformation area, which may be calculated using the formula below.

$$Young's modulus = \frac{Slope}{Film\ thickness \times Cross\ head\ speed} \times 100 \qquad (3)$$

7.8 Folding endurance

Folding endurance is another method for determining a film's mechanical qualities. It's calculated by folding a film at the same location over and over until it breaks. The number of times the film can be folded without breaking is known as the folding endurance value. A film with a higher folding endurance rating has better mechanical strength. The mechanical strength of films and their folding durability are inextricably linked. Because plasticiser concentration influences mechanical strength, it is apparent that plasticiser concentration also has an indirect effect on folding endurance.

7.9 Swelling index

Film swelling tests are carried out with a simulated saliva solution. Each film sample is weighed and put in a stainless steel wire mesh that has been pre-weighed. In a plastic container, the mesh containing the film sample is immersed in a 15 ml medium. The weight of the film was measured at predetermined intervals until it reached a consistent weight.

$$Swelling\ index = \frac{Increase\ in\ weight\ of\ film - Initial\ weight\ of\ film}{Initial\ weight\ of\ film} \times 100 \qquad (4)$$

7.10 Moisture content and uptake

Films that have been previously weighed are kept in a desiccator for 24 hours. When the weight of each film does not change anymore, the final weight is recorded. The following formula may be used to calculate the percentage of moisture content.

$$\%Moisture\ content = \frac{Initial\ weight\ of\ film - Final\ weight\ of\ film}{Initial\ weight\ of\ film} \times 100 \qquad (5)$$

The test is carried out by storing previously weighed film in desiccators at a certain temperature and relative humidity level. The film is removed after three days and reweighed to estimate the percentage of moisture absorption [66]. The following formula may be used to calculate the percentage of moisture uptake.

$$\%Moisture\ uptake = \frac{Final\ weight\ of\ film - Initial\ weight\ of\ film}{Initial\ weight\ of\ film} \times 100 \qquad (6)$$

7.11 *In vitro* dissolution study

Under standardised circumstances of liquid/solid interface, temperature, and solvent concentration, dissolution is defined as the quantity of drug material that enters the solution per unit time. For dissolving testing, any of the pharmacopoeia's standard basket or paddle apparatus can be utilised. The dissolving medium will be chosen based on the sink circumstances and the greatest dosage of API. The temperature of the dissolving media should be kept at 37 ± 0.5°C and the rotational speed at 50. The paddle device has the problem of causing oral films to float above the dissolving liquid when used [71].

8. Conclusion

In recent years, medication formulation into various films has become increasingly popular. The development of innovative polymeric thin films as a drug delivery platform has been pushed by several unwanted problems associated with current dosage forms, such as inconvenient administration, poorer bioavailability, and patient non-compliance. Because of the versatility of this dissolvable film technology platform, it has the potential to be used in a variety of pharmaceutical, biopharmaceutical, and medical sectors in the future. It also allows current pharmaceuticals whose patents are about to expire and will shortly be subject to generic competition to extend their revenue life cycles. In other words, oral films provide product lifetime management. Furthermore, the bulk of the production processes is well-understood and controllable, resulting in a stable and efficient transition from bench to market. The businesses are working to develop a variety of thin films for use in the oral, buccal, sublingual, ophthalmic, and transdermal routes. As a result, polymeric thin films are predicted to stand out as a dosage form as an alternative to traditional dosage forms, overcoming the limits provided by existing dosage forms. Finally, the thin-film technology combined with the chosen medication component must obtain widespread public acceptability, paving the path for other medicines to adopt this portable, extremely handy pharmaceutical form. As new technologies for preparing thin films are quickly launched, the future of film technology appears to be bright.

Authors' contributions

I declare that this work was done by the authors named in this article. RJ conceived and designed the study, WA carried out the literature collection of the data, RC did the writing and NG corrected the manuscript. The authors read and approved the final manuscript.

Competing interests

The authors declare no competing interest.

Consent for publication

Not applicable.

Availability of data and materials

All the information in the manuscript has been referred from the included references and is available upon request from the corresponding author.

Abbreviations

FDA	Food and Drug Administration
GRAS	Generally Recognised as Safe
DDS	Drug delivery system
TDDS	Transdermal drug delivery system
RT	Residence time
HPMC	Hydroxypropyl methylcellulose
HPC	Hydroxypropyl cellulose
CMC	Carboxymethyl cellulose
PVA	Poly (vinyl alcohol)
EMA	European Medicines Agency
CNS	Central nervous system
GI	Gastrointestinal tract
HEC	Hydroxyethylcellulose
SCMC	Sodium carboxymethyl cellulose
PVP	Poly(vinyl pyrrolidone)
API	Active pharmaceutical ingredient
3D	Three-dimensional space
SEM	Scanning Electron Microscopy

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