Insights into medicated films as attractive dosage forms

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Abstract:

Different traditional dosage forms available in the market with many drawbacks including patient inconvenience, limited applications to several sites, variable bioavailability in addition to patent expiration. These drawbacks make pharmaceutical companies look for other drug platforms. Thin films loaded with active ingredients which are prepared as flexible polymer layer gaining acceptability in drug industry. They are easily prepared, adapted for administration of drug via different routes (to overcome several barriers) including ocular, dermal, transdermal, vaginal, oral and others. In additions, thin films are free of harmful chemicals and offer good drug stability. This review spotlights on the medicated thin films as alternative dosage forms that require further attention to maximize their performance and application.

Key words: thin film, polymer, buccal, transdermal, local effect.

تسليط الضوء على شكل جرعة الفلم العلاجي

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الخلاصة:

تتوفر أشكال جرعات تقليدية مختلفة في السوق مع العديد من العيوب بما في ذلك إزعاج المريض ، والتطبيقات المحدودة لعدة مواقع ، والتوافر البيولوجي المتغير بالإضافة إلى انتهاء الصلاحية. هذه العوائق تجعل شركات الأدوية تبحث عن منصات أدوية أخرى. الأغشية الرقيقة المحملة بالمكونات الفعالة التي يتم تحضيرها كطبقة بوليمر مرنة تكتسب القبول في صناعة الأدوية. يتم تحضيرها بسهولة وتكييفها لإعطاء الدواء عبر طرق مختلفة (للتغلب على العديد من الحواجز) بما في ذلك العين والجلد وعبر الجلد والمهبل والفم وغيرها ، بالإضافة إلى أن الأغشية الرقيقة خالية من المواد الكيميائية الضارة وتوفر استقرارًا جيدًا للأدوية. تسلط هذه المراجعة الضوء على الأغشية الرقيقة العلاجية كأشكال جرعات بديلة تتطلب مزيدًا من الاهتمام لتعظيم أدائها وتطبيقها.

الكلمات المفتاحية: الافلام الرقيقة، بوليمر، فموي، عبر الجلد، تاثير موضعي.

Introduction

The term "thin film" is often used to describe a flexible polymer layer that may or may not include a plasticizer [1]. Being naturally thin and pliable, they may be less noticeable and more acceptable to the patient [2]. To function effectively as a drug release platform, The thin film is made of polymers, that fulfills numerous conditions[3]. Fundamentally, thin films are promising alternatives to tablets and liquid formulations for addressing sensitive sites [4]. It has been shown that thin films may speed up the beginning of therapeutic action, decrease the need for multiple

dosing, and increase medication efficacy. The substantial metabolism produced by proteolytic enzymes may be eliminated or much reduced with the use of thin films because it promote local absorption of proteins/peptides and to offer stability and improvement of the permeability profile along the gastrointestinal tract [5]. Drug to be included in the film should have the following properties, among others: a good drug loading capacity; a quick dissolution rate; a lengthy residence duration at the site of administration[6]. An ideal thin film should also display appropriate formulation stability, they have to be biodegradable, biocompatible, and free of harmful chemicals [7]. Thin film formulations also provide a number of benefits such as, non-invasive administration, simple manufacturing, transportation and low research costs [8].

As a result of a paradigm change in manufacturing technique and a large variety of appropriate polymers, a diverse set of thin films has been developed [9]. Therefore, as a new drug delivery dosage form, a thin film is gaining appeal and acceptability in the pharmaceutical industry. Polymeric thin films for buccal, sublingual, ophthalmic, and topical delivery have been the subject of much research and development[10]. In recent years, the use of thin films to administer drugs sublingually or via the buccal mucosa has been receiving attention[11]. Likewise, ophthalmic films are being developed to circumvent the ocular barriers and stop medication loss through the lacrimal drainage system [12]. Polymers of varying grades may be controlled in terms of their composition, allowing for the change of crucial aspects of thin films such as drug release rate, mucoadhesive qualities, mechanical strength, and related properties. Fillers, plasticizers, saliva stimulating agents, colorants, and sweeteners are some examples of the inactive components that may be added to enhance the product's visual qualities. Although several unique works and patents have been published in recent years, more research into how to maximize thin film performance is still necessary [13].

limitations of thin films

Low drug load for a delivered drug of less potency to be given at high dose may be a significant barrier to the widespread use of thin films. Hygroscopicity is a common property of thin films, therefore, more care has to be taken if they are to be kept for a prolonged period of time[14] . In oral film formulation, it is difficult to combine many drugs since doing so slows down either the dissolve rate or the disintegration time of each individual medication [15]. Excessive drying time is a major issue during the manufacture of oral film formulations. Complete drying at normal temperature takes about a day which significantly slowing film production. Since hot air ovens are not advised for drying thermolabile pharmaceuticals, other methods of drying should be applied such as freeze drying, which like any other, has its own limitations. Freeze drying is expensive in terms of both capital and operational costs.

Polymers used in the preparation of thin film

Polymers are the fundamental component of film formulations, and there is a wide variety of polymers available for use in the production of thin films. The polymers that are used must not be hazardous or irritating, and they must not include any contaminants that may leak into the environment. Film formers are typically water-soluble polymers, and used to produce a thin film with rapid disintegration, high mechanical strength, and sensory effects on the mouth that are favorable. For the creation of films, both natural and synthetic polymers are utilized [16].

There is such a wide variety of polymers available, therefore, specialized qualities may be imposed onto thin films. For example, gelatins may have a variety of molecular weights; hence, it is possible to

make attractive and glossy films by using gelatin that has an increased molecular weight. Pullulan is commonly used in the production of film that is very thin because of its remarkable solubility, high mechanical strength, and stability across a broad range of temperatures [17].

A thin film that had an outstanding mechanical strength was produced when chitosan was mixed with either high methoxy pectin (HMP) or low methoxy pectin (LMP). Because of their hydrophilic nature, film-forming polymers such as hydroxypropyl cellulose (HPC), methyl cellulose, and carboxymethyl cellulose (CMC) make a water vapor barrier-weak film. This is owing to the fact that these polymers help retain water [11]. Methocel E3, Methocel E5, and Methocel E15 Premium LV were the three grades of HPMC that were used as the principal film former in the preparation of a fast-dissolving film containing triclosan for use in one particular research endeavor. The result of the research indicated that Methocel E5 Premium LV when employed in a measured quantity 2.2% weight-per-volume (w/v) was capable of producing films with high film qualities [18]. When compared to films that simply included HPMC E15, the in vitro residence period of the film that was formed from Carbopol®934P and HPMC E15 was nearly twice as long[19].

Polymer combinations in film preparation also shown enhanced durability. Producing fast-dissolving films for oral administration that include insoluble drugs like piroxicam requires the use of maltodextrins (MDX) with a low dextrose content as a film-forming polymer. These films were intended for oral administration. In spite of the fact that the medication was loaded into the film in the form of a powder, the resultant film was quickly disintegrating and flexible enough to withstand some stretching without breaking[20]. This was the case despite the fact that the ductility of the film had decreased.

In a similar manner, increasing polymer content had significant effect on the mechanical properties, as well as their physical properties. For example, granisetron HCl Oral Disintegrating Films was prepared using HPMC and pullulan. Pullulan with concentrations of 40-45% proved unable to generate films with excellent strength, but HPMC utilized in concentrations of 40% produced films that were difficult to peel. The stickiness of the film increased when the concentration of HPMC was more than 50% [21]. Examples of polymers commonly used in film formulations are listed in table 1.

Table (1): Examples of polymers commonly used in film formulations

Class	Examples
Cellulose ethers	Hydroxypropyl methylcellulose (HPMC) Hydroxypropyl cellulose (HPC) Hydroxyethyl cellulose (HEC) Methylcellulose (MC) Methylhydroxyethylcellulose Ethylcellulose Sodium carboxymethylcellulose
Vinyl derivatives	Polyvinyl pyrrolidone (PVP) Polyvinyl alcohol (PVA) Polyvinyl pyrrolidone - polyvinyl acetate copolymers Glycols Polyvinyl alcohol - polyethylene glycol copolymers
Glycols	Polyethylene glycols
Acrylic polymers	Methacrylate aminoester copolymer Ethylacrylate-methylmethacrylate copolymer
Other carbohydrates	Maltodextrin Polydextrose

Excipients used in film preparations

Plasticizers

Typically, the plasticizers are used in the concentration of 0- 20% w/w of dry polymer. Plasticizer is an important ingredient of the film to improve the flexibility of the film and reduces the bitterness of the film by reducing the glass transition temperature of the film. The selection of plasticizer depends upon the compatibility with the polymer and type of solvent employed in the casting of film. Plasticizers should be carefully selected because the use of improper plasticizers and its concentration affect the mechanical properties of the film. PEG 400, Propylene glycol, Glycerol, castor oil is most commonly used plasticizers.

Penetration enhancers

Penetration enhancers are also the important excipients to be added in the buccal film formulation. These are required when a drug has to reach the systemic circulation to exert its action. These must be nonirritant and have a reversible effect. The epithelium should recover its barrier properties after the drug has been absorbed. The most common classes of buccal penetration enhancers include fatty acids (that act by disrupting intercellular lipid packing) as well as surfactants, bile salts, and alcohols[22].

Coloring agents

To improve the elegant appearance of films, coloring agents suc as FD & C approved coloring agents are incorporated in the formulation[23]. Some marketed films are presented in table 1:

Table (2): A list of some marketed films[24]

Product Name	Manufacturer	Active Product Ingredient (API)
Benadryl	Pfizer	Diphenylhydramine HCL
Triaminic	Novartis	Phenylephrine HCI
Klonopin Wafers	Solvay	Clonazepam
Gas-X	Novartis	Simethicone

Applications of thin films

Ocular drug delivery

Generally, over 90% of ocular preparations such as eye drops (solution or suspension) or ointments are available in the market. But these preparations may not have a positive effect on treatment outcomes [25]. Regular dosage with eye drops is required for medications used to treat eye disorders. Most frequently, this results in patients refusing medication or requiring intermittent dosage. It is typical for drugs to reach the circulation through the nasolacrimal duct even when they are applied topically to the eye, which might result in harmful adverse effects[26]). Increasing ocular bioavailability and lowering the obstacles to ocular medication administration are driving the popularity of ophthalmic film development.

Ophthalmic films provide for more effective treatment with less systemic adverse effects. Therefore, ocular films may have promising prospects as a system for the pharmaceutical drug's distribution to replace the regular dosage forms for the purpose of obtaining both high effectiveness of treatment and patient acceptability. The constant movement of tears over the outer surface of the cornea acts as an impediment to the diffusion of medicines, which in turn results in a poor bioavailability (between 1 - 7 percent) [27]. In most cases, the medicine that has a greater lipophilicity will run into numerous difficulties since it is insoluble in the watery environment of the eye. Because of the pain that the medicine creates in the eye, it stimulates blinking, which in turn causes considerable amounts of the drug to be washed out of the eye. Therefore, knowledge of the substance in its entirety is essential for the development of films intended for the eyes, the restrictions to ocular drug administration, as well as the excipients that are utilized. Therefore, when it comes to the creation of ocular films, all of these elements should be taken into consideration. Some ocular films are listed in table 2.

Table (3): A list of some marketed ocular film drugs[19]:

Film-active agent	Brand name
Ganciclovir	Vitrasert®
Fluocinolone acetonide	Retisert®
Dexamethasone	Ozurdex®

Transdermal drug delivery

Films has been employed for transdermal delivery of steroidal hormones, analgesics, local anesthetics, and anti-emetics with the purpose of producing systemic effects [28]. Transdermal film delivery is used for few medications due to the fact that the bioavailability of the drug is affected by a number of factors. These factors include the molecular size of the drug, its polarity, the pka of the drug, the state of hydration

level of the skin, the subcutaneous reservoir of drug, and drug metabolism by skin flora. To a similar extent, the hydration of skin is essential for improving medication absorption, and this is made possible by the incorporation of humectant into the formulation of the film. The physiological parameters that determine the overall result of the therapeutic actions of the medicine include the regional skin location, the type of the stratum corneum, skin thickness, and appendage density [29]. When compared to other conventional transdermal dose forms, such as patches or gels, the thin film could have a higher therapeutic effectiveness and be more readily accepted by patients due to the fact that they are easier to apply, more flexible, and have a superior aesthetic look[30] . Some examples on marketed transdermal films are listed in table 3.

Table (4): A list of some marketed transdermal films[31].

Brand name	Manufacturer
BandAid® Sprühpflaster	Ethicon GmbH, Germany
Dermabond®	Ethicon GmbH, Germany
Flint® Sprühverband	Togal, Germany

Vaginal drug delivery

Vaginal drug delivery is increasing for local as well as systemic diseases. The vaginal pathway is good for getting many drugs into the body because it has a significant surface area, enough blood flow, and no hepatic first-pass effect [30]. Due to its anatomical and physiological features, the vagina may be employed as an alternative to parenteral delivery for peptides and proteins [31]. There are a lot of obstacles in creating a vaginal formulation. Considerations include culture, sanitation, gender, local irritation, and sexual participation[32]. The vaginal tract's self-cleaning activity lowers the residence time of creams, gels, suppositories, and pills, causing leaks and messes [32]. Meeting functional characteristics such as, product dispersal through vagina, prolonged residence time, proper physicochemical interaction with all of vaginal material, release strategy of active components, and target results [33]. In mucoadhesion, both natural and artificial macromolecules stick to biological tissue that has been covered with mucus [34]. It has been investigated whether or if the therapeutic advantages of vaginal medicine administration systems using mucoadhesive polymers might be increased [35]. Some polymers, such as kappa carageenan (in vitro absorption inhibitor), carbomers (in vivo HIV cell binding interference), cellulose acetate phthalate (inactivates HIV and HSV in vivo), and polystyrene sulfonate (PSS), are microbicidal (activity against HIV and HSV, in vitro).

With the development of polymer technology, polymeric vaginal films are used to deliver medications to the genital area, satisfying the needs of patients (33). Vaginal films are polymeric drug delivery systems that may be placed without the need for an applicator. They typically have a square form with a soft and homogenous surface and have sides that are around 5-10 cm in length. They're flexible enough to be folded and inserted vaginally. Water-soluble polymer films are very thin films, these dosage forms disperse/ disintegrate when inserted in the vaginal canal, releasing the active pharmaceutical components [34]. To prevent mechanical injuries during insertion, it is the purpose of modern films to immediately disperse or dissolve upon contact with fluids, creating a smooth surface, a thick, sticky,

biocompatible gel while still maintaining a pleasing appearance (ideally being colorless and odorless), pliability, softness, and the lack of any sharp edges. These advantages should make the vaginal insert easier to implant, increase user acceptance and compliance, and provide a bioadhesive dispersion that stays there for a long time [35].

Formulations for vaginal films often include the active ingredient, as well as water-soluble polymers, plasticizers, fillers, and color. The selected polymers should not be poisonous, did not irritate the skin, free of leachable contaminants, have excellent wetting qualities and spread ability, have strength that is satisfactory in peeling, shearing, and tensile testing, and should be economical to make and pack. Common polymers used in the creation of vaginal films include polyethylene glycol, polyvinyl alcohol, and cellulose derivatives[36]. For example, the currently available in the United States, Apothecus Pharmaceutical's vaginal contraceptive film (VCF) is a film that has 28% nonoxynol-9 in a polyvinyl alcohol basis. Examples that have been extensively researched are contraceptives and microbicides [37].

Gastro retentive drug delivery

An extended drug delivery system, or gastroretentive delivery system, allows more time for the medicine to remain in the stomach (GRT). This approach targets the stomach and upper small intestine, but it is generally recognized that the stomach's limited surface area limits the absorption of nutrients and medicines into the systemic circulation, whereas the duodenum, jejunum and ileum are the most critical sites for absorption [38]. Preparing controlled release gastro-retentive cinnarizine films is an example of a film preparation used as a gastro-retentive dosage form. The film was folded and placed usually in a capsule and once it is in the stomach, it will be unfolded with time until complete folding achieved and keep its integrity all the time in the stomach, as shown in figure 1 [39]. Based on a non-Fickian diffusion mechanism, the polymeric film showed rapid drug release in the first hour and then a more constant release over the following 12 hours [40].

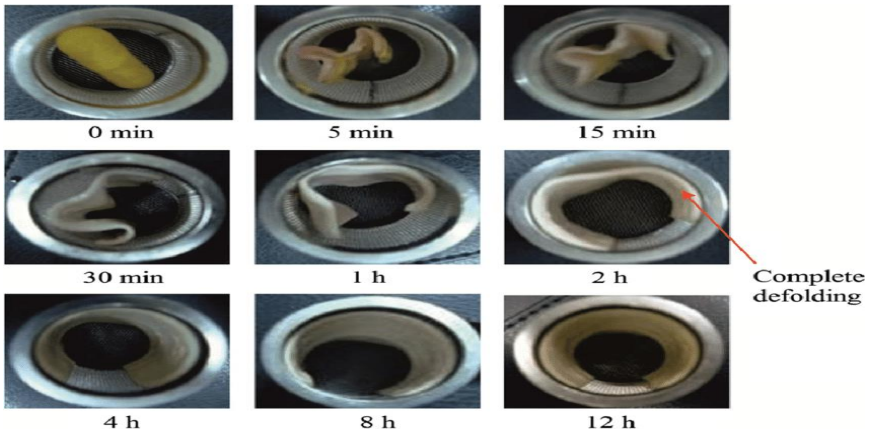

Figure (1): **Unfolding behavior of film.**

In a different experiment, furosemide was used to create a floating, expandable gastroretentive film [41]. Ginger extract also for the treatment of GI diseases was formulated into gastroretentive expandable films for controlled release. The films were made by placing a starch/chitosan composite sheet in a solid dispersion of ginger extract, folding the sheet, and inserting it inside a hard gelatin capsule [42]. Films need low concentrations of active ingredients and may be made in a variety of ways, including the solvent casting technique, rolling, hot-melt extrusion, semisolid casting, and solid dispersion extrusion [43]. Numerous natural

and synthetic polymers can be used to prepare gastroretentive film such as different grades of HPMC like HPMC15000cps, HPMC K4M, HPMC E5, carpabol 934 and sodium alginate [44].

Oral drug delivery

Oral thin film (OTF) is "containing one or more active pharmaceutical ingredients (APIs), an elastic and non-brittle strip that is put on the tongue prior to passing into the gastrointestinal system, aiming for a fast break down or disintegrating in the saliva," as described by the FDA". Zuplenz (Ondansetron HCl, 4-8 mg) was the first OTF to be licensed for prescription use and was introduced in 2010. Suboxone, which contains buprenorphine and naloxone, was authorized very immediately after the first drug. According to the available data, oral dissolving and disintegrating dosage forms are preferred by four out of five patients over more conventional oral solid dosage forms[45].

The development of polymeric films has made it feasible to increase the medication's effectiveness in terms of both bioavailability and patient compliance when administered orally, particularly via the buccal and sublingual routes. Buccal mucosa is a good drug delivery channel because to its advantageous anatomical and physiological properties, such as the presence of smooth muscles with high vascular perfusion, simple accessibility, and passing of first pass metabolism [46]. These characteristics can be found in the buccal mucosa. Lips, cheeks, tongue, hard palate, soft palate, and the floor of the mouth make up the components that make up the oral cavity. When compared to other mucosa, the permeation of the medications is higher via the buccal and sublingual pathways [47].

Buccal mucosa is 10 times more permeable to water than skin. Similarly, a hydrophilic medication was discovered to be able to pass through the oral mucosa 4–4000 times more easily than it could through the skin [48]. In the treatment of acute conditions, the administration of a medicine via the sublingual route is preferred because it is optimized for the distribution of drugs with high permeability across the mucosa. On the other hand, when a longer release of the medicine is necessary, the buccal route is preferable for the treatment of chronic diseases [49]. The internal jugular vein provides a direct route to the body's systemic circulation once medicine is administered buccally. Systemic pharmaceutical delivery through the mouth may be challenging because of the oral environment and biological restrictions. In order for the drug to enter the systemic circulation after being delivered locally (sublingually or buccally), it must first be released from its formulation and travel to the site of administration. Fluid volume, pH, enzyme activity, and oral mucosa permeability affect medication absorption in the oral mucosa. Saliva secretion reduces medication residence duration at the delivery location owing to washout. Swallowing medications may occur before oral absorption [50]. For greater therapeutic bioavailability and patient adherence, these points should be considered while producing oral formulations like polymeric films.

The polymeric mix films would offer a comfortable and adaptable platform for medication administration in the mouth [51]. Buccal films are now being used for a wide range of medications, including anti-inflammatory medicines, analgesics, anesthetics, proteins, and peptides. Drugs in Class II of the Biopharmaceutics Classification System (BCS), such as opioid analgesics like fentanyl citrate, may be delivered transmucosally by buccal administration (tradenamed as Onsolis®/Breakyl®), has become increasingly common in recent years. For the purpose of medication delivery, mucoadhesive films have been used. In a similar manner, the mucoadhesive film does not detach the buccal region, resulting in reduced inter- and intra-individual variability [46]. Disintegrating systems are

similar to oral thin films (OTFs), which become sticky when exposed to saliva and dissolve in the mouth. The medicine is released at a quick pace due to the breakdown process, and then absorbed via the oromucosa. This method of administration is used for many medications that are broken down in the digestive system [52].

By using a variety of polymers, OTFs may acquire highly tailored characteristics. Varied types of gelatins have different molecular weights, which means that glossy, visually appealing films with a high molecular weight may be produced using gelatin. Making a thin film out of pullulan is a widespread procedure, that is both mechanically strong and soluble, and it is stable across a broad temperature range. When high-methoxy pectin is combined with chitosan or low-methoxy pectin, an ultra-thin film is produced with exceptional mechanical strength. Polymers with hydrophilic structures, such as methylcellulose, hydroxypropyl cellulose, and carboxymethyl cellulose, produce a thin film upon contact with water, which then spreads and/or expands. Combining polymers and the characteristics of the resulting OTFs are listed in Table 2 (19) .

The first products to use oral thin films for commercial distribution were nutraceuticals and OTC medications; these products' active ingredients, which may include vitamins, herbal or non-herbal extracts, were already familiar to consumers. As a thin film product designed to refresh the mouth, Pfizer created Listerine pocketpaks® in 2001. Bio-film is a firm that has been working on developing thin films for use in the mouth. They are employing both medications and nutraceuticals, such as vitamins, health supplements, energy boosters, and hunger suppressors, to reach a certain demographic within a given age range. The energy booster is made up of a number of different ingredients, including caffeine, guarana, and green tea extract, all of which work together to keep energization (53).

Multiple companies have been working on a polymeric-film-based medication delivery system. Most of them have previously obtained a film that provides both faster release and enhanced therapeutic effects [54]. Oral thin films (OTF) are divided into three categories [55].

- Flash discharge (quick release), such as paroxetine oral fast dissolving film [56].
- Mucoadhesive disintegrate (mucoadhesive quick release), such as estradiol mucoadhesive oral film [57].
- Sustained-release mucoadhesive (mucoadhesive extended-release), such as nystatin mucoadhsive sustained release oral film [58]. Some distinguished features for oral thin films according to their categories are listed in table 2.

Table (5): Features of oral thin film's according to their behavior and release profile [59] .

Features	Quick release oral thin film	Mucoadhesive quick release oral thin film	Mucoadhesive extended-release oral thin film
Area (cm^2)	2-8	2-7	2-4
Thickness (mm)	20-70	50-500	50-250
Structure	Single layer	Multilayer or single	Multilayer
Excipients	Water-soluble polymers	Water-soluble polymers	Low-solubility or insoluble polymers
Pharmaceutical phase	Solid or dissolved/ dispersed	Drug molecule in solid or suspended form	Suspension, solid or dissolved/ dispersed
Application area	Lingual	Buccal or gingival region	Alternate sites in the mouth and gums
Dissolution	60 second	Gel consists in minutes	8-10 hour maximum
Effect	Local or systemic	Local or systemic	Local or systemic

Conclusion

The development of an elegant medicated thin films that suited different routes of administration including ocular, transdermal, vaginal, oral as well as buccal and gastroretentive makes these films as alternative dosage forms that can be used as alternative for the conventional dosage forms having undesirable drawbacks such as administration inconvenience, low bioavailability and patient non-compliance. The future looks very promising towards the application of film technology in a wide variety of drug delivery system.**z**

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