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Review

Thin films as an emerging platform for drug delivery

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ABSTRACT

Pharmaceutical scientists throughout the world are trying to explore thin films as a novel drug delivery tool. Thin films have been identified as an alternative approach to conventional dosage forms. The thin films are considered to be convenient to swallow, self-administrable, and fast dissolving dosage form, all of which make it as a versatile platform for drug delivery. This delivery system has been used for both systemic and local action *via* several routes such as oral, buccal, sublingual, ocular, and transdermal routes. The design of efficient thin films requires a comprehensive knowledge of the pharmacological and pharmaceutical properties of drugs and polymers along with an appropriate selection of manufacturing processes. Therefore, the aim of this review is to provide an overview of the critical factors affecting the formulation of thin films, including the physico-chemical properties of polymers and drugs, anatomical and physiological constraints, as well as the characterization methods and quality specifications to circumvent the difficulties associated with formulation design. It also highlights the recent trends and perspectives to develop thin film products by various companies.

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1. Introduction

Generally, thin films can be referred as a thin and flexible layer of polymer with or without a plasticizer [1]. Since they are thin and flexible by their nature, it can be perceived to be less obtrusive and more acceptable by the patient [2]. The thin film is polymeric matrices that meet many requirements for being used efficiently as a drug release platform [3]. Fundamentally, thin films are excellent candidates for targeting sensitive site that may not be possible with tablets or liquid formulations [4]. Thin films have shown the capabilities to improve the onset of drug action, reduce the dose frequency and enhance the drug efficacy [3]. Similarly, thin films may be useful for eliminating side effects of a drug and reducing extensive metabolism caused by proteolytic enzymes [5,6]. Ideal thin films need to exhibit desirable features such as sufficient drug loading capacity, fast dissolution rate or long residence time at the site of administration, and acceptable formulation stability. They should also be non-toxic, biocompatible and biodegradable [7,8].

Compared with the existing traditional dosage forms, it stands out to be superior in terms of enhanced bioavailability, high patient compliance, and patent extension of active pharmaceutical ingredients (API) [9]. Furthermore, thin film formulations offer several advantages, including (a) convenient administration through non-invasive routes, (b) ease of handling during manufacture and transportation, and (c) cost-effectiveness in the development of formulations [8,10,11]. The availability of a wide array of suitable polymers and the paradigm shift in manufacturing technology have made possible to develop a wide range of thin films [12]. Therefore, a thin film is gaining popularity and acceptance in the pharmaceutical arena as a novel drug delivery dosage form.

Substantial efforts have been made to formulate polymeric thin films that are administered generally *via* buccal, sublingual, ocular and skin routes [13,14]. Among different routes, the use of thin films for delivering medicine into sublingual or buccal mucosa has drawn immense interest in recent years [15]. Meanwhile, ophthalmic films are currently developed for overcoming the ocular barriers and preventing loss of drugs through the lacrimal drainage system [16]. Controlling compositions of polymers of different grades has facilitated the modification of key characteristics of thin films such as drug release rate, mucoadhesive properties, mechanical strength and other related properties. Additionally, various inactive components can be included such as fillers, plasticizer, saliva stimulating agent, colorants, and sweeteners for improving aesthetic characteristics. Many pharmaceutical companies are fascinated by the appealing features of thin films, and as a result they have already patented various technologies for producing thin films [17].

Currently, a significant amount of original works and patents can be found in literature, but still there is a need for extensive studies to optimize the performance of thin films accurately. The lack of appropriate guidance for the manufacture, characterization and quality control of the thin films has sought the need of adequate studies in this area from the pharmaceutical viewpoint. Therefore, this paper will contribute to give insights on understanding the critical quality attributes and characterization methods with the aim to enhance the performance of thin films.

2. Types of thin films

Thin film is not a recent formulation, and it was first introduced in late 1970 to overcome swallowing difficulties exhibited by tablets and capsules [15]. Various names of thin films appeared, such as oral film (oral thin film), oral soluble film, wafer, oral strip, orodispersible film (ODF), buccal film, mucoadhesive film, ophthalmic film, and transmucosal film. While several films are designed to be dissolved quickly in the oral cavity for the absorption of a drug in the gastrointestinal cavity (oral and oral soluble, or orodispersible films), some are prepared to deliver a drug at the site of administration (e.g., buccal, sublingual and ophthalmic thin films). Drugs with high mucosal permeability have been known to be suitable for buccal and sublingual delivery with films [18]. Likewise, ophthalmic thin films are generally applied to treat diseases of the anterior segment such as conjunctivitis, glaucoma and chronic dry eye syndromes [5,19].

A film that readily dissolves in the oral cavity is generally termed as orodispersible film according to European Medicines Agency (EMA) or simply soluble film according to FDA [3]. Usually, fast dissolving oral films are ultra-thin film (50–150 μm) having size of postage stamp, which dissolves within a minute in the oral cavity after being in contact with the saliva, resulting in quick absorption and instant bioavailability of the drugs [20,21]. Drugs loaded in buccal adhesive films are absorbed directly *via* buccal mucosa, which delivers the drug to the systemic circulation after their absorption [22]. Likewise, wafer is frequently mentioned as paper-thin polymeric films employed as carriers for pharmaceutical agents. This innovative dosage form is taken orally but does not require water to swallow for the absorption of a drug [23]. Orodispersible films should not be misunderstood with buccal films designed for staying longer on the cheek mucosa [24]. Therefore, different types of films should be distinguished accurately to prevent possible misinterpretations.

3. Advantages of thin films as an emerging dosage form

3.1. *Advantages over conventional dosage forms*

A thin film dissolves rapidly than other conventional dosage forms [25]. Thin films are less friable and easy to carry dosage form compared to commercialized orally fast disintegrating tablets, which need special packing. Likewise, a single dose of strip can be carried individually without requiring the secondary container [26,27]. It is very important to address the poor stability of liquid dosage forms, especially the aqueous formulations. Unlike the thin films, there is a need for great care during accurate measurement of the amount and shaking the bottle every time before administration may contribute to less acceptance by the patients [3]. Conventional ophthalmic drug delivery systems such as eye drops or solutions are commonly used but they are limited in their ability to provide high ocular drug bioavailability and sustained duration of action [28]. Ophthalmic thin films can be used to improve the drug delivery to the eye. In contrast to transdermal patch, the transdermal film is less associated with skin irritation due to less

occlusive properties that improve the water vapor permeation through the skin and do not leave sticky sensation on the site of application [29,30].

3.2. *Clinical advantages*

Patients show preference toward thin film due to its appellative form and ease of administration [17]. Furthermore, oral dissolving film is extensively useful for pediatric, geriatric, and psychiatric patients since it is easy to administer and avoid the risk of choking or suffocation, thus ensuring patient safety [22]. Ophthalmic films have been known to enhance the retention time of a drug, and thereby the absorption of the drug was greatly improved from the anterior segment of the eye [31]. Moreover, the polymeric thin films can also be beneficial for bedridden and non-cooperative patients as they can be administered easily and hardly spit out. A thin film is useful in cases where a rapid onset of action is required, such as in motion sickness, sudden episodes of allergic attack or coughing, bronchitis or asthma [22].

4. Major limitations of thin films

Use of thin films is sometimes limited largely due to low drug loading capacity for a less potent drug given at high dose [10]. Thin films are usually hygroscopic in nature. Thus, special precaution should be taken for their longer preservation [4]. Combining more than one drug concomitantly is a very challenging task in oral film formulation because both the dissolution rate as well as the disintegration time are hindered by the co-administration of a drug in oral films [32]. The difficulty to obtain a high degree of accuracy with respect to the amount of drug in individual unit dose of the film can lead to therapeutic failure, non-reproducible effects and sometimes toxic effects to the patient [33]. Preparing oral film formulation is concerned with the issues of requiring excessive time for drying. It takes around one day for the complete drying at room temperature, which notably decreases the rate of production of films. Since it is not recommended to use hot air oven for thermolabile drugs, an alternative process of drying should be explored [22].

5. Polymers for the preparation of thin films

Polymers are the backbone of film formulations and various polymers are available for the preparation of thin films [34]. The polymers can be used alone or in combination with other polymers to achieve the desired film properties. The polymers employed should be non-toxic, non-irritant, and absence of leachable impurities is required. Water-soluble polymers are used as film formers to produce a thin film with rapid disintegration, good mechanical strength, and good mouthfeel effects. Both natural and synthetic polymers are used for film preparation [20,35]. The list of polymers commonly used in the manufacture of polymeric films, with additional descriptions and properties, is depicted in Table 1.

Availability of diverse polymers allows imparting specific properties in the thin films. For instance, gelatins are available in different molecular weights, and thus the appealing and glossy films could be obtained with the gelatin having a high molecular weight. Pullulan is frequently used for producing a thin film with great solubility, high mechanical strength and they are stable over a wide range of temperatures. The blending of chitosan and high methoxy pectin (HMP) or low methoxy pectin (LMP) resulted in a thin film exhibiting an excellent mechanical strength. The film forming polymers such as hydroxypropyl cellulose (HPC), methyl cellulose, and carboxymethyl cellulose (CMC) produce a thin film with less water vapor barrier due to hydrophilic nature which aids in water retention [15].

In one study, a fast-dissolving film of triclosan was prepared using different grades of hydroxypropyl methylcellulose (HPMC) named as Methocel E3, Methocel E5, and Methocel E15 Premium LV as a primary film former. The result demonstrated that Methocel E5 Premium LV at the concentration of 2.2% w/v produced films with excellent film properties [37]. The *in vitro* residence time of the film made from Carbopol® 934P and HPMC E15 was almost double than the films containing only HPMC E15. Additionally, it was observed that the combined polymers were more resistant to breakage [11]. Cilurzo et al. reported the use of maltodextrins (MDX) with low dextrose content as a film forming polymer for the preparation of oral fast-dissolving films of an insoluble drug, piroxicam. Despite the decrease in film ductility due to the loading of the drug as a powder, the produced film exhibited satisfactory flexibility and resistance to elongation along with rapid dissolution [38]. Similarly, oral dissolving films of granisetron HCl manufactured using HPMC and pullulan illustrated the effect of increasing polymer concentration on mechanical properties and physical properties of films. Pullulan with 40–45% concentration was not able to produce films with good strength whereas the HPMC used in 40% concentration yielded the film which was difficult to peel. Likewise, the film stickiness increased when the concentration of HPMC was beyond 50% [39].

Mucoadhesive films are thin and flexible retentive dosage forms, and release drug directly into a biological substrate. They facilitate in extending residence time at the application site leading to prolonged therapeutic effects [40]. Majority of the thin film having mucoadhesive properties are hydrophilic in nature and undergoes swelling and form a chain interaction with the mucin [11]. Among the several studied polymers, the most compelling mucoadhesion properties are exhibited by chitosan, hyaluronan, cellulose derivatives, polyacrylates, alginate, gelatin and pectin [41]. Compared with non-ionic polymers, the cationic and anionic polymers facilitate strong interaction with mucus [42]. Anionic polymers are well characterized due to the existence of carboxyl and sulfate functional groups, which create the negative charge at pH values surpassing the pKa of the polymer. As an example, sodium carboxymethyl cellulose (NaCMC) and polyacrylic acid (PAA) exhibit excellent mucoadhesive properties because of bond formation with the mucin [43]. Thiomers, i.e. polymer containing thiol group, stand out to enhance mucoadhesion because they are able to interact with the mucin through the formation of disulfide linkages. The process of 'thiloation' is possible with many polymers, using amide-coupling chemistry, where the aqueous solvent systems are used [44]. Eudragit displayed promising mucoadhesive properties when used alone or in combination with other hydrophilic polymers. Films, prepared from the propranolol HCl,

Table 1 – Properties and key findings of representative polymers used for preparation of thin film formulations.

Polymer	Properties	Key findings	References
Hydroxypropyl methylcellulose (HPMC)	• White, creamy, odorless, and tasteless powder • Mw 10,000–1,500,000 • Soluble in cold water, but insoluble in chloroform and ethanol • Viscosity (η) 3–100,000 mPa·s • Non-ionic polymer with moderate mucoadhesive properties • Solutions are stable at pH 3.0 to 11.0	• Film forming ability at 2–20% concentrations • Generally used for controlled and/or delayed release of the drug substance • Initial burst drug release followed by slow or sustained drug release diffusion observed in buccal bioadhesive system of nicotine hydrogen tartrate	[3,11,17,36]
Carboxymethyl cellulose (CMC)	• White, odorless powder • Mw 90,000–700,000 • Easily dispersed in water to form a clear or colloidal solution • η 5–13,000 mPa·s (1% aqueous solution) • High swelling properties • Good bioadhesive strength	• Improved the residence time of HPC and sodium alginate films • Good compatibility with starch forming single-phase polymeric matrix films with improved mechanical and barrier properties • The enzymatically modified CMC has good film forming property	[3,11,17,36]
Hydroxypropyl cellulose (HPC)	• White to slightly yellow colored, odorless, inert and tasteless powder • Mw 50,000–1,250,000 • Soluble in cold and hot polar organic solvents such as absolute ethanol, methanol, isopropyl alcohol and propylene glycol • η 75–6500 mPa·s depending upon the polymer grade • Moderate mucoadhesive properties	• Used to replace synthetic polymers or HPMC in a polymer matrix with modified starch to improve solubility • It has a good film forming property and 5% (w/w) solution is generally used for film coating • Zero-order release kinetics of lidocaine and clotrimazole associated with erosion square-root of time release kinetics of lidocaine	[3,11,17,36]
Poly (vinyl pyrrolidone) (PVP)	• Wide range of solubility • Non-ionic • High swelling properties • Used as co-adjuvant to increase mucoadhesion	• Blending of PVP with PVA and HPMC improves film forming ability • Blended with ethyl cellulose and HPC produces films with increased flexibility, softer and tougher properties • Different ratios of PVP-alginate blends can be used to design drug controlled release • As film-forming polymer exhibited non-Fickian release of ketorolac and progesterone	[3,11]
Poly (vinyl alcohol) (PVA)	• White to cream-colored granular powder • Mw 20,000–200,000 • Water soluble synthetic polymer • Non-ionic polymer • Moderate mucoadhesive properties	• Very flexible films • Mainly used in ophthalmic polymeric preparations at concentration of 3–5% • Higher elongation at break values	[3]
Poly (ethylene oxide) (PEO)	• Non-ionic polymer • High mucoadhesion with high molecular weight	• Optimization of tear resistance, dissolution rate, and adhesion tendencies of film by combining low Mw PEO, with a higher Mw PEO and/or with cellulose • Films with good resistance to tearing, minimal or no curling • Pleasant mouth feeling with no sticky or highly viscous gel formation	[3,11]
Pullulan	• White, odorless, and tasteless powder • Mw 8000–2,000,000 • Soluble in hot as well as cold water • η 100–180 mm^2/s (10% aqueous solution at 30 °C) • Contain > 6% w/w of moisture	• Blending with sodium alginate and/or CMC may synergistically enhance the properties of the film • Pullulan–HPMC films have improved thermal and mechanical properties • 5–25% (w/w) solution forms flexible films • Stable film with less permeability to oxygen	[3,17]
Pectin	• A yellowish white, odorless powder with mucilaginous taste • Mw 30,000–100,000 • Soluble in water but insoluble in most of the organic solvents • Strong mucoadhesive properties	• Not very useful for fast dissolving films, but modified pectins yielded films with fast dissolution rates • Good film forming capacity at low temperature • Brittle and do not have a clear plastic deformation	[3,17]
Chitosan	• White or creamy powder or flakes, and odorless • Obtained after partial deacetylation of chitin • Biocompatible and biodegradable • Sparingly soluble in water; practically insoluble in ethanol (95%), other organic solvents, and neutral or alkali solutions at pH above approximately 6.5	• Excellent film forming ability • Chitosan enhances the transport of polar drugs across epithelial surfaces • Possesses cell-binding activity due to polymer cationic polyelectrolyte structure that binds to the negative charge of the cell surface	[11,36]

(*continued on next page*)

Table 1 – (*continued*)

Polymer	Properties	Key findings	References
Sodium alginate	• Occurs as a white or buff powder, which is odorless and tasteless • Purified carbohydrate product extracted from brown seaweed by the use of dilute alkali • Insoluble in other organic solvents and acids where the pH of the resulting solution falls below 3.0 • η 20–400 Cps (1% aqueous solution) • Anionic with high mucoadhesive properties • Safe, biodegradable and non-allergenic • Rapid swelling and dissolution in water	• Used as immobilization matrices for cells and enzymes, controlled release of bioactive substances • Excellent gel and film forming properties • Compatible with most water-soluble thickeners and resins	[11,36]
Carrageenan	• An anionic polysaccharide, extracted from the red seaweed *Chondrus crispus* • Three structural types exist: Iota, Kappa, and Lambda, differing in solubility and rheology • The sodium form of all three types is soluble in both cold and hot water • The best solution stability occurs at pH 6 to 10 • Moderate mucoadhesive properties	• Potential to act as protein/peptide stabilizer by steric stabilization • It is compatible with most nonionic and anionic water soluble thickeners • Solutions are susceptible to shear and heat degradation	[6,11,36]
Gelatin	• A light amber to faintly yellow colored powder • Mw 15,000–250,000 • Soluble in glycerin, acid, alkali and hot water • η 4.3–4.7 mPa·s (6.67% (w/v) aqueous solution at 60 °C) • Moisture content 9–11% (w/w)	• It has a very good film forming ability • Useable for preparation of sterile film, ophthalmic film, and sterile sponge	[17]

Eudragit RS100, and triethyl citrate (plasticizer), demonstrated mucoadhesive force three times greater than the film prepared with chitosan as the mucoadhesive polymer [11]. Juliano et al. prepared a buccoadhesive films consisting of alginate and/or HPMC and/or chitosan either as a single polymer or in a combination of two. Basically, they aimed the films to release the chlorhexidine diacetate in a controlled manner. HPMC was not able to prolong the chlorhexidine release as more than 80% of the drug was released within only 30 min. However, chlorhexidine incorporated in alginate and alginate/chitosan-based films showed that only 30–35% of the drug was released in 30 min; hence, this polymeric system is beneficial for prolonged drug release [45].

In common terms, polymers are understood as excipients, but it has become an essential component while designing and formulating thin films. Therefore, understanding the properties of polymers such as chemistry, rheology, and physicochemical properties of polymer seems to be imminent for maximizing their uses to develop a thin film. The selection of appropriate polymer during the development of polymeric thin films may be critical; thereby, several points should be considered according to the requirements. Therefore, it is imperative to consider the appropriate polymer for producing a thin film with a better performance that assures high therapeutic success.

6. Technologies for manufacturing thin films

The most commonly used techniques for the preparation of thin films are solvent casting [46,47] and hot melt extrusion [38,48]. However, an innovative technique like inkjet printing [49] has evolved in the past few years. Various methods that have been employed for polymeric thin film manufacturing are described below in detail:

6.1. *Solvent casting*

Among several techniques of film manufacturing, solvent casting is feasible, preferable and undoubtedly widely used method mainly due to the straightforward manufacturing process and low cost of processing. The manufacturing procedure of thin films with the solvent casting method along with the quality control parameters in each step is illustrated in Fig. 1. The rheological properties of the polymeric mixture should be taken into account since they affect the drying rate, the film

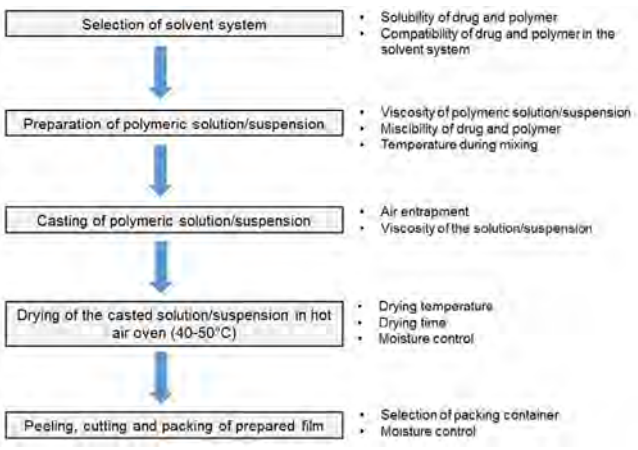

Fig. 1 – Solvent casting method for film preparation with quality control parameters in each step.

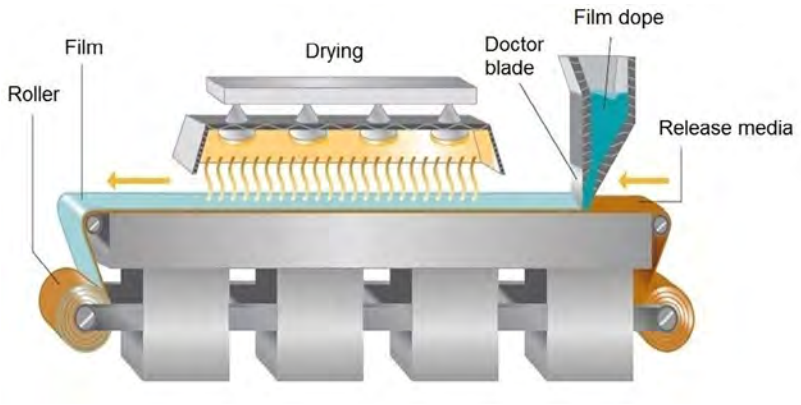

Fig. 2 – Commercial manufacturing of film based on solvent-casting (reproduced from Ref. [22]).

thickness, the morphology as well as the content uniformity of the films [26]. The mixing process could introduce the air bubbles into the liquid inadvertently; therefore, de-aeration is a pre-requisite to obtain a homogeneous product [17]. After casting the solution into a suitable substrate, they are left for drying to allow the solvent to evaporate, which just leaves a polymeric film with a drug on it [2].

After the complete drying of the film, it is cut into suitable shape and size depending upon the required dosage of the formed strip. In the majority of the cases, the strips are rolled and stored for a certain time before cutting, which is known as 'rollstock' in an industry. However, a film should not be exposed for too long time since it is prone for being damaged. If possible, it should be cut and packed immediately after the preparation to keep its stability [17]. Several advantages such as better physical properties, easy and low cost processing, and excellent uniformity of thickness are observed with the film obtained by solvent-casting [50]. However, this process suffers from some limitation. For instance, a polymeric thin film prepared by solvent casting method was brittle upon storage, as marked by decrease in the percent elongation due to evaporation or loss of the residual solvent in the film over time [51]. Another issue under scrutiny associated with this method is the requirement of using organic solvents. The presence of organic solvent system is a serious problem because it causes a hazard to health and environment. As a result, strict regulations have been adopted by many countries regarding the use of an organic solvent [11].

Translating the production of films from a bench scale to production scale is one of the biggest challenges because many factors such as heating, mixing speed, and temperature could bring variability in quality, and consistent formation of films in commercial scale may not be possible. Therefore, sufficient endeavor should be invested to optimize the various parameters such as the speed of casting, drying time, and final thickness of the dried strip, which may affect the production of films from commercial scale output [17]. Fig. 2 depicts the machine that is used for a large-scale production of film based on solvent casting technique.

6.2. *Hot-melt extrusion (HME)*

HME is a versatile method adopted for the manufacture of granules, tablets, pellets [52], and also thin films [38]. It is a substitute method to solvent casting for the preparation of the film, especially useful when no organic solvent system is required [10]. However, only few literature has reported the use of hot-melt extrusion for the preparation of polymeric thin films [11]. HME is a process of shaping a mixture of polymers, drug substance, and other excipients into a film by melting all the components [3]. Eventually, the films are cut into a particular shape and dimensions [6]. In this method, a mixture of pharmaceutical ingredients is molten and then charged through an orifice (the die) to obtain homogeneous matrices [11]. Since APIs are subjected to operation at high temperature with complete absence of solvents, this method is not suitable for thermos-labile APIs [17]. The practical steps of HME are outlined as follows [53]:

(1) Feeding of the components to the extruder through a hopper,
(2) Mixing, grinding, and kneading,
(3) Flowing the molten and blended mass to the die, and
(4) Extruding the mass through the die and further downstream processing.

The equipment for the process of HME is illustrated in Fig. 3, which consists of the hopper, extruder, film die, and roller. The extruder contains one or two rotating screws (co-rotating or counter rotating) inside a static cylindrical barrel. The barrel is often manufactured in sections to shorten the residence time of the molten material. The sectioned part of the barrel is either

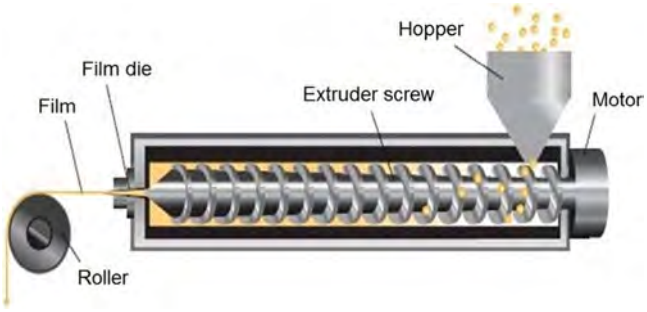

Fig. 3 – Hot-melt extrusion system for the preparation of films (reproduced from Ref. [22]).

bolted or clamped together. Similarly, the end portion of the barrel is connected to the end-plate die, which is interchangeable depending upon the required shape of the extruded materials [1].

With regard to the advantages of HME, it produces a drug in the form of solid dispersion or solution, which could improve solubility of poorly soluble drugs [51]. However, at elevated temperature, there is a high chance of recrystallization of API in the polymer blend as the temperature drop. Using highly viscous polymeric substance or increasing the amount of plasticizer can prevent this problem. Another issue of HME is the "Die swell phenomenon," i.e. an increase in the cross-section of the film after ejection from the die depending on the viscoelastic characteristics of polymers. This is due to the polymer withstanding high energy kneading and high shear force during extrusion. This problem can be prevented by slowing the speed of screw operation or by gently mixing molten mass for a long time instead of high shear kneading for a short duration [54]. Unlike solvent casting, this method avoids the need of organic solvent; hence, they are proven to be environment friendly [2].

6.3. *Printing technologies*

Novel methods such as 3D printing could be used for manufacturing polymeric thin films. It could potentially be a platform for producing the dosage form beneficial to the individual patient. This possibly will resolve the issue of the pharmaceutical industry and pharmacies to meet the future demand of customized medicine [55]. The printing technologies are increasingly gaining popularity because of its flexibility and cost-effectiveness. From the viewpoint of pharmaceutical industry, printing technologies are commonly in practice for identifying or labeling of the pharmaceutical dosage forms, particularly to optimize the product to be readily identified and to prevent counterfeit production. However, this approach has recently been adopted for the drug loading of pharmaceutical dosage forms [3]. The examples include the use of off-the-shelf consumer inkjet printers in which drug-loaded inks are deposited to yield accurately dosed units of pharmaceutical ingredients. In addition, a combination of inkjet and flexographic technologies has been practiced as well [55]. The inkjet printing was used for printing of API on different substrate, whereas the flexographic printing was employed to coat the drug loaded-substrate with a polymeric thin film [56].

Loading of drug substances into transdermal patches is possible *via* screen printing and pad printing; however, pad printing is limited by the low speed of production. In recent years, inkjet printing has made inroads for preparation of film formulation as a safe and accurate method to produce dosage form of potent drug administered at low dose [57]. Preparation of multiple layers can be done by adding a second printing layer on the top of the first with or without an intermediate base film layer. Further, the printed layer would be shielded by a second base film layer. This will result in modified drug release profiles and protect the ink layer from detachment or mechanical stress during processing like cutting or packaging area [55].

Regardless of the various types of printing technique used, all of them contribute to producing a film with more homogeneous distribution and accurate dosage of the drug throughout the films. The dose accuracy and uniform distribution of the drug substances in the films are accounted for several reasons, such as coating mass properties, like viscosity or density, which are inherently influenced by the amount and characteristics of the processed drug substances. With regard to the conventional method of film preparation, it may be very challenging to ensure the same dosage accuracy in the individual units [3]. To summarize, printing a drug on dosage form is the latest intervention for film preparation and it has become a powerful tool to manufacture dosage form with excellent uniformity, speed-ability, and stability. Representing printing technologies that have been used for preparation of polymeric thin films are discussed below.

6.3.1. *Inkjet printing*

Inkjet printing is the recently developed technology, which is characterized by its versatility, accuracy, repeatability and relatively inexpensive method that deposits small volumes of solution in films. Inkjet printing is extensively applicable for the preparation of low dose medicines and also offers an opportunity to manufacture personalized medicines [58].

Inkjet technology is usually divided into mainly two types: (a) continuous inkjet printing (CIP) and (b) drop on demand (DoD) printing. Both are different in their printing process by which the drops are generated. In the case of CIP, there is a consistent ejection of a liquid through an orifice (nozzle), and it breaks up into a stream of drops under the force of surface tension. For the continuous production of a stream of inkdrops, the individual drop should be 'steered' to a particular landing site to produce a printed pattern. This is possible by applying an electric charge on some of the drops that deflect the stream from the main axis under an electrostatic field. On the other hand, ejection of the liquid from the printhead occurs in drop-on-demand printing only when a drop is needed. The production of individual drop takes place rapidly under the response of trigger signal. A DoD printhead consists of multiple nozzles (ranges from 100 to 1000, even though specialist printhead may have a single nozzle). The drop ejection occurs due to the kinetic energy of drops generated from the source located in the printhead nearby to each nozzle [59].

The uniform distribution and dose accuracy of the drug substance in the film rely upon the density or viscosity of the ink (drug substance solution or suspension), which determine the printability characteristics [3]. Janßen et al. demonstrated the deposition of low doses of salbutamol sulfate onto commercially available starch-based film using conventional desktop printers [10]. However, inkjet printing is not applicable for high-throughput industrial production, instead using of flexographic printing is regarded more suitable for industrial preparation.

6.3.2. *Flexographic printing technology (FPT)*

FPT is a process that transfers active pharmaceutical ingredient into thin films gently *via* contact printing [10]. The flexographic printing is a rotary printing process as depicted in Fig. 4, where ink consisting of drug substance solution and suspension is measured by an anilox roller, then are transferred to a printing cylinder that prints the film after unwinding the daughter roll [3]. It is useful for heat sensitive products like proteins and peptides. As the mixing and drying of film formulation are processed before introducing the drug, the problems such as loss of activity of API can be prevented. The production efficiency is also high considering the production

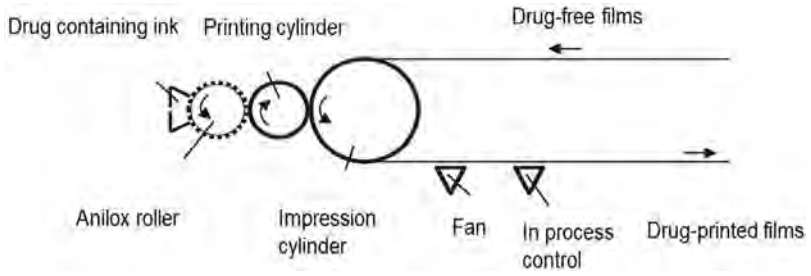

Fig. 4 – Schematic overview of flexography technology for the preparation of films (reproduced from Ref. [57]).

rate of 530 oral films per minute; hence, this process could be expanded to scale-up production [6]. No effect on the mechanical properties of polymeric thin films upon printing drug solutions was witnessed using flexographic printing [57]. In a study, Janßen et al. found that it was possible to dispense tadalafil and rasagiline mesylate solution onto hydroxypropyl methylcellulose films using flexographic printing. The introduction of hydroxypropyl cellulose appeared to reduce drug crystallization after printing. However, the main drawbacks of flexography are relatively low resolution, high chances of contamination, and the need to prepare a print roller, which is not suitable for large scale production [10].

7. Quality issues of thin films

For being regarded as an ideal thin film, a film should have adequate flexibility, softness, elasticity, and good physicochemical stability. Therefore, all these parameters should be considered carefully while developing film to ensure its efficient performance. Characterization of a film is a pre-requisite that may include assessing properties such as mechanical strength, hydration, *in vitro* release and surface morphology. The following section outlines the various critical quality attributes affecting film properties and commonly used *in vitro* methods for film characterization.

7.1. *Thickness and weight variation*

The measurement of thickness is necessary as it directly correlates with the amount of drug in the film. In addition, an appropriate thickness is required for the comfortable administration of films. For instance, the ideal thickness of buccal films should be in the range of 50 to 1000 μm [12]. Generally, the thickness of the formed thin films is measured using Vernier caliper, electronic digital micrometer, screw gauge, or scanning electron microscopy (SEM) images [60,61]. The amount of plasticizer in the formulation is known to increase the film thickness slightly [62]. By inserting m (Batch) – the mass of the whole batch, m (API/film) – the drug amount per film, ρ (Batch) – the density of the formulation, m (API) – the total drug amount in the batch and A (Film) – the area of one film in Eq. (1), it is possible to calculate the casting thickness (h). A correction factor f is added due to the shift of actual value of film thickness compared to the set values. A shift behavior is defined beforehand over different coating thicknesses [63].

$$H\,(\mu m) = \frac{m\,(\text{Batch}) \times m\,(\text{API/film}) \times 10{,}000}{\rho\,(\text{Batch}) \times m\,(\text{API}) \times A\,(\text{Film})} + f \quad (1)$$

where API is active pharmaceutical ingredient, m is mass, ρ is density, and A is area expressed in g, g/cm^3, and cm^2 respectively.

The weight variation is generally determined to ensure that each film contains the consistent amount of a drug without significant deviation. It is calculated by weighing the individual film and the average weights of specified films respectively. The average weight of film is subtracted from the individual weight of patches. The mean ± SD values are calculated for all the formulations. A large variation in weight signifies the inefficiency of the method applied and high chances are there for non-uniformity in drug content [12].

7.2. *Mechanical and physical properties*

Polymeric films should possess enough tension so that it can be ejected easily from the pouch, rolled up after casting, and peeled from the release liner, but should not be too flexible because greater elongation during cutting and packaging might cause variation in film amount resulting in non-uniformity of API amount per film [49,64]. Mechanical properties of films can be defined in terms of Young's modulus, percent elongations, tensile strength and tear resistance [64,65]. It has been known that soft and weak polymers exhibit low tensile strength, low elongation at break and low Young's modulus, whereas the hard and tough polymer have a high tensile strength, high elongation at break and high Young's modulus [11]. Additionally, the mechanical properties of films are affected by the method of manufacturing and the formulation. Some general behaviors of films observed from stress—strain curves are shown in Fig. 5 [6]. The concentration and types of the polymers are largely responsible for producing a film having good mechanical strength and integrity [66]. Likewise, the morphological state of the film may alter the mechanical strength, e.g. by crystal growth [64]. Therefore, different factors such as film-forming agent, type of manufacturing process, thickness of film and the type and amount of API in the film have to be considered carefully for controlling the mechanical strength of the film.

Blending and cross-linking of two or more polymers are useful methods to improve the mechanical properties of the combined polymeric mix [67]. The film maintains their appearance and integrity after cross-linking, but hardening of the film surface can occur [68]. Consistent with this observation, the mechanical properties of PVA–NaCMC films were greater

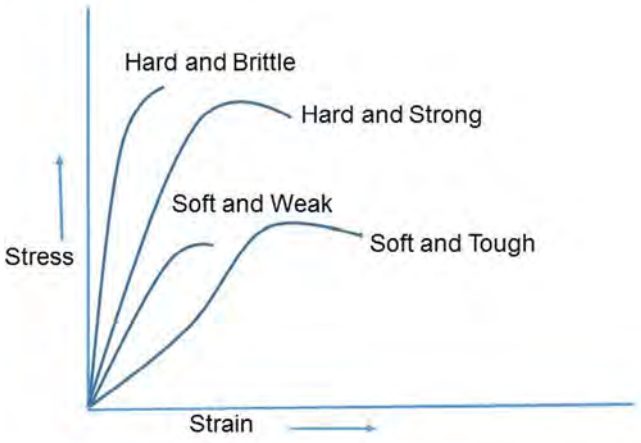

Fig. 5 – Examples of stress–strain curves obtained from polymeric thin films (reproduced from Ref. [11]).

than film composed of PVA or NaCMC alone. The tensile strength of PVA–NaCMC film was found to be 13 to 17 times greater than those of films made of the synthetic polymer N-vinylpyrrolidone [69,70]. Use of plasticizer may overcome the brittleness and soften the rigidity of the film structure by reducing the intermolecular forces. The most commonly used plasticizer are glycerol, sorbitol, propylene glycol and polyethylene glycol [66,71]. However, using too much amount of plasticizer can decrease the adhesive strength of films by overhydrating the film formulations [72]. For example, glycerin intercalates themselves between every individual strand of polymer, thereby causing disruption of polymer–polymer interaction. The tertiary structure of the polymers is changed into more flexible and porous type. For this reason, the plasticized polymer deforms at lower tensile strength compared with a polymer without plasticizer [73].

In most of the works of literature, the most commonly used method for characterizing the mechanical strength of a polymeric film is carried out by using texture analyzer. The system starts measuring force and displacement of the probe when they are in contact with the sample. There is an individual sample holder to aid measurement of small-sized film samples (Fig. 6). Films are attached by screws between two plates with a cylindrical hole of required diameter. The plate is stabilized to avoid movements using pins, which are placed centrally beneath the punch. The adjustment can be made to move the probe forward according to required working velocity. The measurement starts after the probe is in contact with the sample surface (triggering force). The movement of probe occurs at constant fixed speed until the film detaches. At last, the applied force and displacement (penetration depth) should be recorded along with the room temperature and relative humidity [64]. During the measurement of mechanical strength using texture analyzer, it was found that the contact time, contact force, and the speed of probe withdrawal markedly influence the experimental outcome [74]. The tensile strength is calculated by using several parameters such as folding endurance, percent elongation, elongation at break and Young's modulus.

7.2.1. *Folding endurance*

The flexibility of thin film is important when considering that the films can be administered without breakage. The flexibility of the polymeric thin films can be measured with respect to its folding endurance. The folding endurance is determined by folding the film repeatedly at 180° angle of the plane at the same place until it breaks. The film exhibiting folding endurance value of 300 or more is considered to have excellent flexibility [75].

7.2.2. *Percent elongation and elongation at break*

Elongation, a kind of deformation, is a simple change in shape that any objects encounter under any applied stress. In other

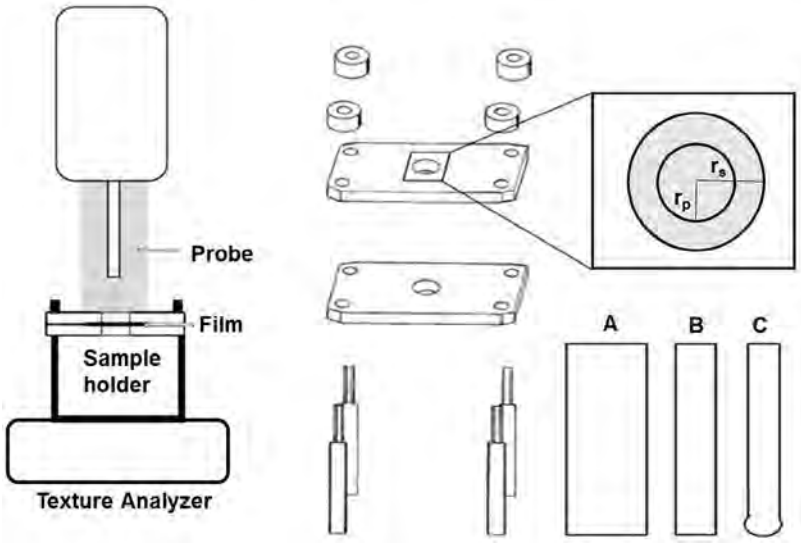

Fig. 6 – Experimental setup (left) and sample holder for the film preparation (right), where r_s indicates radius of samples, and r_p indicates radius of probe. Geometry of cylindrical probes A and B and spherical probe C is shown on the right bottom (reproduced from Ref. [64]).

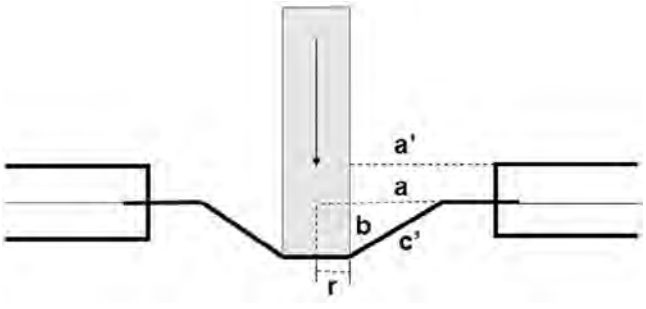

Fig. 7 – Determination of percent elongation of thin films using a texture analyzer, where a = initial length of the film in the sample holder opening, a' = initial length – radius of probe, *b* = displacement of the probe, c' + r = length after strain, c' = length of a' after strain, r = radius of the probe [64].

words, when the sample is subjected to tensile stress, deformation of the sample takes place resulting in stretching or elongation of sample [17]. Measurement of elongation is generally done to predict the ductility of polymers [65]. Elastic elongation or elongation at break of a sample can be measured by using a texture analyzer. Elastic elongation is a phenomenon shown by all kinds of elastomers. The percent elongation indicates the stretch ability of material without being broken, whereas elongation at break means the point until which the film can be stretched when it is torn (or broken) by the applied probe (Fig. 7). With the exertion of stress to a sample, strain generates, and the sample elongations will become more predominant as the amount of stress applied increases. After reaching a certain point, the sample breaks; this point of breakage is referred to as percent elongation break [76]. The formula for percent elongation is given in Eq. (2) as under:

$$\%\ \text{Elongation} = \frac{\text{Increased length of film}}{\text{Initial length of film}} \times 100 \quad (2)$$

Elongation at break can also be calculated by using following formula as well:

$$\text{Elongation at break}\ (\%) = \left(\frac{\sqrt{a'^2 + b^2 + r^2}}{a} - 1 \right) \times 100 \quad (3)$$

where a is the initial length of the film in the sample holding opening, a' is the length of the film not punctured by the probe, b is the penetration depth/vertical displacement by the probe, and r is the radius of the probe (Fig. 7) [64].

7.2.3. *Young's modulus*

Young's modulus or elastic modulus reflects the stiffness or elasticity of the films. This indicates resistance to deformation of the films, which can be calculated by plotting the stress strain curve, where slope indicates the modulus, i.e. the greater the slope, the greater would be the tensile modulus. On the other side, the small slope means lesser tensile modulus and deformation [77]. Simply, a film, exhibiting higher tensile strength and greater Young's modulus values, is the one that is hard and brittle with small elongation. Texture analyzer can be used for the measurement of Young's modulus, where slope is obtained from the stress strain curve. Young's modulus is represented as the ratio of applied stress over strain in the region of elastic deformation, which can be determined using the following formula:

$$\text{Young's modulus} = \frac{\text{Slope}}{\text{Film thickness} \times \text{Crosshead speed}} \times 100 \quad (4)$$

A range of crosshead speed can be obtained by changing the speed of the motor of the texture analyzer [15].

7.2.4. *Tear resistance*

The property of the film to withstand the rupture is known as tear resistance. The measurement of tear resistance is done by allowing the film to undergo a constant rate of deformation. The maximum force or stress needed to tear the film is measured in Newton or pound-force [17]. In a stress strain curve, the area of the plot measures the tear resistance. The relation of an area under the stress strain curve is directly proportional to the toughness of the film, i.e. higher area of the plot means higher toughness of the film and also greater amount of energy that a material can absorb. Therefore, it measures the strength of the material rather than toughness. In fact, a less strong material can be tougher compared with a strong material and no confusion should be created [12].

7.3. *Moisture content*

The amount of moisture in the film could be crucial as it affects the mechanical strength, adhesive properties, and friability of film [78]. Several factors are responsible for elevating water level such as hygroscopic properties of API, polymers, and solvent system used to dissolve the polymeric mixture, and manufacturing techniques. In general, the moisture content of the film is determined by using several methods like Karl Fischer titration or by weighing method. In weighing method, preweighed films (initial weight) are heated at a temperature of 100–120 °C until they attain constant weight. Finally, the weight of the final dried sample is taken. Eq. (5) is used for calculating the amount of moisture content in the film that is expressed as % moisture and is given below [12]:

$$\text{Moisture content}\ (\%) = \left[\frac{(\text{Initial weight} - \text{Final dried weight})}{\text{Initial weight}} \right] \times 100 \quad (5)$$

7.4. *Swelling*

Swelling properties of films are generally observed as the polymers employed for making films are hydrophilic [79]. Swelling of the polymers is known to be the fundamental step required for bioadhesion [80,81]. In many cases the degree and rate of swelling play a key role in controlling the release of the drug. Hence, these parameters can be considered as the indicator for bioadhesive or mucoadhesive potential and drug release profiles. The testing of swelling is done to measure polymer hydration [82]. Hydrophilic polymers with different structures possess a varying degree of swelling based on the

relative resistance of matrix network structure to water molecule movement. For example, a polymer chain having the low ability to form hydrogen bond is unable to form a strong network structure, and water penetration is also difficult to occur. When the number of hydrogen bonds as well as the strength between the polymers increase, the diffusion of water particles into the hydrated matrix occurs at a slow rate [83]. This was demonstrated by Panomsuk et al., where it was reported that the introduction of mannitol to methylcellulose matrix decreases the swelling index of the membrane. This may be due to the formation of hydrogen bonding between drugs and the polymeric matrix [84].

Measuring swelling or degree of hydration of the polymeric film plays an important role in providing key information on the mucoadhesive strength. As we know, the hydration of polymers is the reason for relaxation and interpenetration of polymeric chain; however, the overhydration results in a decrease of mucoadhesion properties due to formation of slippery mucilage [85]. The swelling properties of films, i.e. water absorption capacities, are measured by evaluating the percentage of hydration. For example, the piece of films is weighed (W_1) and it is subjected to immersion in simulated physiological fluid for a predetermined time. After the predetermined time, the sample is taken out, wiped off to remove excessive water on the surface and weighed (W_2). The calculation is done by using the following formula, which is expressed in % [83,86].

$$\text{Hydration}\,(\%) = \frac{W_2 - W_1}{W_1} \times 100 \tag{6}$$

Furthermore, area swelling ratio (ASR) can be used to determine the swelling property of the prepared films. As a procedure, the films are placed in a Petri dish and 100 ml quantity of phosphate buffer (pH = 7.4) was poured into it as a swelling fluid. The diameter of a film is calculated at certain time intervals. The calculation of ASR is based on Eq. (7) [87].

$$\text{ASR} = \frac{A_t}{A_o} \tag{7}$$

where A_t is area of the film at time t, and A_0 is area of the film at time zero.

7.5. *Drug release profiles*

To a great extent, the release kinetics of drugs from the polymer matrix is primarily dependent on the physicochemical properties of the materials used as well as the morphology of the system [36]. Variation in pH or temperature may cause increase or decrease in the erosion or dissolution rates of polymers [88]. Upon contact with biological fluids, the polymeric film starts to swell following polymer chain relaxes, resulting in drug diffusion. The release of drug holds a direct relationship with polymer structure; for example, linear amorphous polymers dissolve much faster than cross-linked or partially crystalline polymers [89]. According to several studies, the release of the drug is markedly influenced by erosion of the film. The degradation rate of the film is also dependent on the types of plasticizer [11]. For the drug to penetrate the biological membrane, the drug should be released from the delivery systems at an optimum rate.

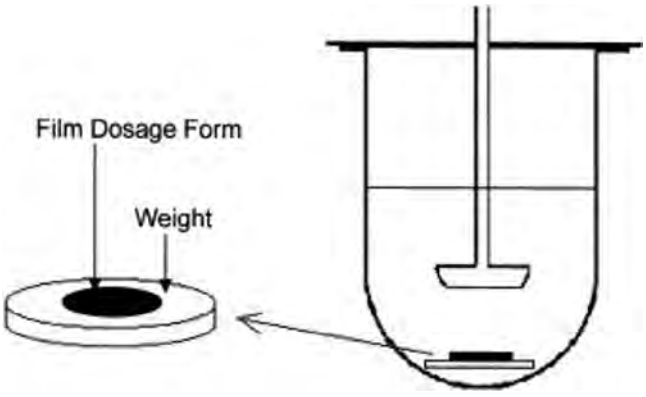

Fig. 8 – Schematic illustration of the apparatus used for dissolution studies of films. The film dosage form (1 cm²) was attached to a 3 cm diameter weight using double adhesive tape (reproduced from Ref. [91]).

Assessing the drug release from the film is essential as it is the rate-determining step in the process of absorption. The dissolution of drugs and/or films is assessed with the apparatus that is approved for other solid dosage forms [90].

In the literature, many authors have done some improvisation on the dissolution apparatus, while others have employed Franz diffusion cells (FDC) for testing the drug release from the polymeric films [12]. A major barrier with respect to film in dissolution testing is the placing of the samples. Several methods have been practiced, where the film is attached on the inner side of the glass vessels or the stirring element using an adhesive tape [24]. Okamoto et al. conducted a dissolution study of lidocaine film for buccal administration using a JP XIII dissolution apparatus at 37 ± 0.1 °C. A film was cut into a circle having an area of 1 cm² and adhered to a 3 cm diameter weight using double adhesive tape. Then, the film with weight was placed in a glass vessel filled with 500 ml of artificial saliva so that the film dosage form faces upwards as shown in Fig. 8 [91].

7.6. *Surface morphology*

The morphology of the film should appear homogeneous and continuous to ensure the uniform distribution of drug throughout the polymeric mixture. Self-aggregation might take place during drying because of the intermolecular and convective forces leading to wrinkled surface in films. Additionally, interaction between drug and polymers, and the crystalline nature of the drug, may result in the formation of rough surface in the films [92]. Hence, assessing the surface morphology and texture is crucial to assure uniform distribution of drugs without any interaction with the polymers in the film formulation. Various surface characteristics such as surface texture (smooth or rough), thickness, and drug distribution (aggregated or scattered) of the film can be observed using light microscopy, scanning electron microscopy (SEM), transmission electron microscopy (TEM) and related imaging techniques [83]. Among all, the scientists have more clung to SEM as a reliable method for examining the surface morphology of the films. The operation is carried out by mounting the films on stubs, sputter coated with gold in an inert environment, and subsequently

the photographs are taken at a suitable magnification. This approach can be utilized for close observation of size, shape and the number of pores on the surface of polymeric films. Most recently, there are a number of studies on the use of SEM in evaluating the role of chemical composition of the film on the crystallinity, morphology and texture [12].

8. Packaging of thin films

Packaging is crucial to provide mechanical protection as well as to keep the stability of thin film formulations. It acts as a barrier to the moisture, light, and oxygen. A number of choices are available for packaging the polymeric thin films, but not all are effective to preserve the integrity and physical properties of the product. Aluminum foils are most commonly used and considered ideal for film packaging as it prevents the film from moisture and light degradation. Similarly, lidding foil has been employed if tamper proof packaging is needed. Films are subjected to multi-track sealing to achieve an accurate airtight seal between the upper and lower pack foils [17]. The most commonly available sizes of films are 3×2 cm^2 and 2×2 cm^2. The packaged films are checked thoroughly before being packed into a secondary packaging container [22]. The packing of manufactured film in foil, paper or plastic pouches is cost-effective, easy to handle, and allows easy formation of the flexible pouch by either vertical or horizontal forming method during product filling [4].

Nowadays, the strips are available in both single dose sachets and multiple-unit blisters. A single dose sachet with a name Pocketpaks™ for cool mint Listerine was introduced by Pfizer consumer healthcare. Similarly, a tear notch/slit/cut-off is manufactured to ensure convenience for the consumer to peel-off the pack. This technique is automated and computer-driven process [17]. APR-Labtec launched a patented packaging system with the name Rapid card for the Rapid® films. The rapid card has same size as a credit card and contains three films on each side, which can be removed individually [22].

9. Routes for the administration of thin films

9.1. *Oral route*

Developing polymeric films has made it possible to improve the drug bioavailability and patient adherence to drug therapy *via* the oral route, especially buccal and sublingual route. The anatomical and physiological characteristics of buccal mucosa, such as the existence of smooth muscles with high vascular perfusion, easy accessibility, and bypassing of first pass metabolism make it a favorable route for the drug delivery [72]. The oral cavity consists of lips, cheek, tongue, hard palate, soft palate and floor of the mouth [2]. Fig. 9 demonstrates the common site for administration of films to buccal and sublingual mucosa. Compared with the other mucosa, the buccal and sublingual routes are preferable because it provides better permeability of the drug [94].

Lesch and co-workers reported the water penetration across the buccal mucosa to be 10 times higher than skin [95]. Similarly, the oral mucosa was found to be 4–4000 times more permeable

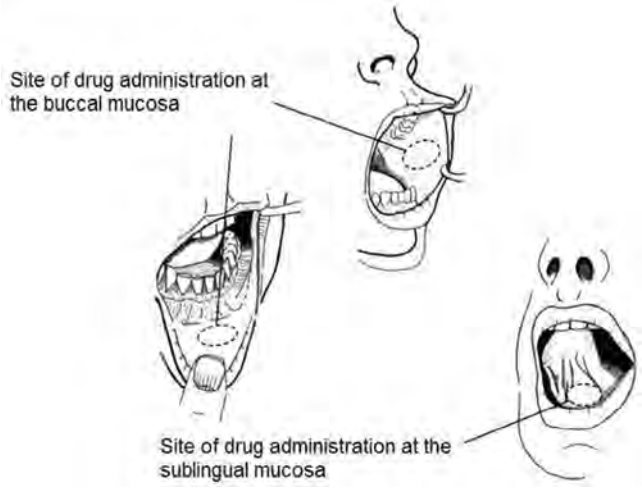

Fig. 9 – Demonstration of common site for application of film in buccal and sublingual mucosa (reproduced from Ref. [93]).

to a hydrophilic drug than the skin [96]. The sublingual route is targeted for the delivery of drug exhibiting high permeability across the mucosa and is utilized for the treatment of acute disorders. On the other hand, the buccal route is preferred for the treatment of chronic disease, when an extended release of the drug is desired [18]. Direct access to the systemic circulation through the internal jugular vein is possible with buccal drug delivery [36].

However, systemic drug delivery in the oral cavity may be extremely challenging due to an unfavorable oral environment and physiological barriers. For achieving a promising therapeutic effect, the drug must be released from the formulation to the delivery site (e.g. sublingual or buccal region) and should penetrate the oral mucosa to reach the systemic circulation. The existence of several environmental related factors such as fluid volume, pH, enzyme activity and the permeability of oral mucosa determines the fate of drug absorption in the oral mucosa. On the other side, the amount of secretion of saliva impedes the residence of drug at the delivery site due to washing out of the drug. Similarly, the swallowing of drugs might occur before the absorption of the drug through the oral mucosa [2,93]. Hence, while developing the oral formulation like polymeric films, all the point should be taken into account for obtaining higher therapeutic bioavailability as well as the patient adherence to the dosage form.

Films containing the polymeric blend would be an ideal platform for the delivery of drugs in the oral cavity because of its comfort and flexibility [97]. Over the last decade, there has been an enormous rise in the development of buccal films as an alternative drug delivery for various classes such as anti-inflammatory, analgesics, anesthetic drugs and proteins and peptides. Of recent, mucoadhesive films have been used as a delivery platform for transmucosal buccal delivery of Biopharmaceutics Classification System (BCS) Class II drugs particularly targeting the opioid analgesics like fentanyl citrate, which is available with a trademark name such as Onsolis®/Breakyl® for treating immense pain [26]. Similarly, the mucoadhesive film remains attached to the buccal area without

Table 2 – List of commercialized thin films for drug delivery.

Company	Brand name	Type of formulation	References
Labtec Pharma	Zolmitriptan Rapidfilm®	Zolmitriptan oral disintegrating films (ODF)	[21]
BioAlliance Pharma	Setofilm®	Ondansetron ODF	
MonoSol Rx and KemPharm	KP106	D-amphetamine ODF	
BioDelivery Sciences International	Onsolis™	Fentanyl buccal soluble films	[11]
Labtec Pharma	RapidFilm®	Ondansetron and donepezil ODF	[2]
Novartis	Triaminic Thin Strips	Phenylephrine and diphenhydramine ODF	[55]
MonoSol Rx	Suboxone®	Buprenorphine and naloxone (sublingual film)	
C.B. Fleet	Pedia-Lax™ Quick Dissolve Strip	Sennosides ODF	
Novartis Consumer Healthcare	Gas-X Thin Strips	Simethicone (sublingual film)	
Pfizer	Sudafed PE quick dissolve strips	Phenylephrine ODF	

showing any erratic absorption profile, resulting in less inter- and intra-individual variability [72]. Oral thin films (OTFs) are comparable to the disintegrating system, which is soaked in saliva and stick to the site of application. The rate of disintegration is rapid, allowing the drug to release and followed by the oromucosal absorption. Many drugs that undergo degradation in the GI tract are being administered employing this route [98].

In context to the commercially marketed product of the oral thin film, the nutraceuticals and over-the-counter drugs were among the first to be introduced in the market, and included the incorporated active such as vitamins, herbal and non-herbal extracts. In 2001, Pfizer introduced a thin film product of Listerine Pocketpaks® developed as mouth freshener. The company Bio-film has been putting an endeavor to develop oral thin films. Not only the pharmaceuticals but they are also using nutraceuticals such as vitamins, aphrodisiac, energy boosters, and appetite suppressor that targets a specific population of the certain age group. The energy booster consists of various compounds such as caffeine, guarana, and green tea extract to maintain the energy levels [17]. A number of companies have been attempting to develop a drug delivery platform based on polymeric films. Most of them have already succeeded in obtaining a film with rapid release along with better therapeutic outcomes [2]. The companies with their technology platform based on polymeric film are listed in the Table 2.

9.2. *Ocular route*

More than 90% of the marketed ocular formulations are in the form of solutions or suspension; however, this conventional dosage form lacks in achieving promising therapeutic success [99]. The frequent instillation of eye drops is needed to elicit a therapeutic response. This usually leads to patient non-compliance and pulsed administration. Furthermore, the topically applied drugs to the eye generally enter the systemic circulation *via* the nasolacrimal duct system, which possibly cause side effects and systemic toxicity as well [100]. With the aim of enhancing the ocular bioavailability and overcoming the ocular drug delivery barriers, the development of ophthalmic film becomes popular these days [84]. The ophthalmic films result in the reduction of dose frequency, less systemic side effects and better therapeutic outcomes. Therefore, ophthalmic films could open exciting opportunities as a delivery platform of therapeutics to replace the traditional dosage forms for achieving high therapeutic success and patient adherence. So far, the list of drugs formulated in ophthalmic films is presented below in Table 3.

The flow of tear across the outer surface of the cornea is continuous, which impedes the drug diffusion leading to low bioavailability (1–7%) of drugs [108]. Generally, the drug with higher lipophilicity encounters many problems as it cannot be dissolved in the aqueous medium of the eye. Since the drug causes discomfort in the eye, it induces blinking, and therefore causing washing out of the significant amount of drug. Therefore, the success of the effective development of films to be delivered to the eye relies on the comprehensive knowledge of the drug, the constraints to ocular drug delivery, and the excipients used. Hence, all these factors should be considered during the formulation of ocular films.

9.3. *Transdermal route*

Drug-loaded transdermal films are the alternative to replace the existing transdermal dosage form. Numerous sustained or controlled delivery systems have been devised, where a drug is either dissolved or dispersed in the films [71]. The film-forming system has been practiced for the transdermal delivery of steroidal hormones, analgesics, local anesthesia and antiemetic for systemic effects [109–111].

Only a small number of drugs are being designed for the transdermal delivery of films as several factors affect the bioavailability of drug such as molecular size, polarity, pH of the drug, state of the skin hydration, subcutaneous reservoir of drug and drug metabolism by skin flora [112]. Similarly, the hydration of skin is crucial for increasing drug absorption, which is possible by using humectant in the film formulation. The physiological factors such as regional skin site, nature of stratum corneum, the thickness of skin, and density of appendages also influence the overall outcome of the therapeutic effects of the drug [113].

Table 3 – List of drugs used in ocular films.

Active agent in ocular film	References
Acetazolamide	[101]
Timolol maleate	[102]
Ofloxacin	[103]
Dorzolamide hydrochloride	[104]
Levofloxacin	[78,105]
Naphazoline HCl	[106]
Natamycin	[107]

The thin film may possess better therapeutic efficacy and patient acceptance compared to the common transdermal dosage forms such as patches or gels [114]. Due to occlusive properties of transdermal patches, it prevents the permeation of water vapor from the skin surface and causes severe pain at the time of peeling. However, polymeric thin films could be a highly promising alternative for transdermal drug delivery because of the ease of application, flexibility and better cosmetic appearance [29].

10. Future scope of development and conclusion

The formulation of a drug into various films has been popular in recent years. Several undesirable drawbacks associated with conventional dosage forms such as inconvenience of administration, lower bioavailability and patient non-compliance have pushed the development of novel polymeric thin films as a drug delivery platform. This drug delivery platform is being under surveillance from both start-up and established pharmaceutical companies. The companies strive to design a wide range of thin films for oral, buccal, sublingual, ocular and transdermal routes. Therefore, as an alternative to conventional dosage forms, polymeric thin films are expected to stand out as a dosage form to overcome the limitations posed by existing dosage forms. The film dosage form encounters several challenges during the phases of formulation development and manufacture. Such issues should be addressed to optimize the overall formulation even after transferring to large-scale manufacturing. The future looks very promising for the film technology in the time to come as new technologies are rapidly introduced to prepare thin films.

Acknowledgments

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