e-ISBN: 978-93-6252-484-3
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THIN FILMS: NOVEL ASPECTS OF DRUG DELIVERY

Abstract

These days, scientists are concentrating their efforts on creating novel dosage forms for thin films in the pharmaceutical industry. Compared to typical dose forms, thin film has become an uncommon dosage type. Thin film has various benefits, including ease of administration, rapid dose release, and patient convenience, all of which make it an excellent choice for medication delivery. This delivery mechanism has been used via a variety of channels, including transdermal, buccal, ocular and oral for both local and systemic movement. Effective film layout necessitates a thorough understanding of the pharmacological characteristics as well as pharmaceutical characteristics of medications and various polymers in addition to the right choice of production techniques. Thus, the aim of this chapter is to provide an detail in depth overview of the key elements influencing the film film components, including the different physico and chemical characteristics of tablets and polymers, physiological limitations, and the optimal specifications and characterization techniques to get around formulation layout challenges. It also showcases the most recent advancements and outlooks for growing thin-film products with the assistance of multiple businesses. Generally speaking, thin films are described as flexible, thin layer of polymer, either with or without a plasticizer. They can give the patient the sensation that they are more ideal and less noticeable because of their natural thinness and flexibility.

Keywords: Thin film, Pharmaceutical, Buccal, Pharmacological, Formulation

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I. BACKGROUND AND INTRODUCTION

The polymeric matrices in the thin film fulfill numerous prerequisites for appropriate utilization as a medication launch platform. In general, thin films are superb options for targeted complex formulations, something that liquid or medicine formulations would not be able to accomplish. Thin films have demonstrated the ability to improve the timing of drug motion, lower dosage frequency, and improve medication efficacy. Furthermore, film films have the potential to mitigate pharmacological side effects and reduce large-scale metabolism resulting from proteolytic enzymes. The greatest films must demonstrate flawless features, such as enough medication loading, a quick dissolving frequency or extended time of residence at the site of administration, and proper system balance. They also need to be biocompatible, biodegradable, and non-poisonous.[3]

In terms of enhanced bioavailability, excellent patient compliance, and patent extension of active pharmaceutical ingredients (API), it is clearly superior to the existing conventional dosage forms. Furthermore, there are several advantages to thin film formulations, such as (a) simple management using non-invasive methods, (b) ease of handling during manufacturing and shipping, and (c) cost-effective formulation development.[4] The availability of a broad range of appropriate polymers and a paradigm shift in manufacturing processes have made it feasible to produce a huge diversity of film films.[4] Because of this, the pharmaceutical industry is starting to find thin films more and more appealing as a single drug delivery dosage form.

Polymeric film films, which are frequently administered topically and delivered via buccal, sublingual, ocular, and cutaneous routes, were created with much effort. Among other novel techniques, the use of thin films for the delivery of medicine to the buccal or sublingual mucosa has attracted a lot of interest lately. Meanwhile, ophthalmic films are being developed to bypass ocular barriers and stop medicine loss through the drainage system of the lacrimal gland.[5] It is now simpler to alter crucial thin-film features including mechanical electricity, mucoadhesive qualities, drug launch cost, and other related attributes by varying the mixture of polymers with various grades. To enhance visual features, a variety of inert additives can be used, including plasticizers, fillers, saliva-stimulating chemicals, colorants, and sweeteners.

Because of their curiosity about the appealing qualities of thin films, a number of pharmaceutical companies have already patented a number of methods for creating thin films.[6] Even if there are now many unique works and patents in the literature, further research is still needed to properly enhance thin film performance overall. The need for adequate pharmaceutical research in this area has been prompted by the lack of guidance for the production, characterisation, and careful handling of film. Thus, in order to improve the overall performance of thin films, this work will contribute to the understanding of the critical superb features and characterisation methodologies.

II. VARIOUS TYPES OF THIN FILM FORMULATIONS

Film was first used in late 1970 to treat swallowing problems induced by drug usage, thus it's not always the newest technology.[7] Numerous additional terms for thin films are taken into account, including transmucosal film, buccal film, mucoadhesive film, ophthalmic

film, wafer, oral strip, oral film, and oral soluble film. Some films, called oral and oral soluble, or orodispersible films, are designed to dissolve quickly in the oral cavity to facilitate the absorption of a drug within the gastrointestinal cavity. Other films, such as buccal, sublingual, and ophthalmic thin films, are structured to supply a drug at the site of administration.

Similarly, anterior phase diseases such glaucoma, chronic dry eye syndromes, and conjunctivitis are commonly treated with ocular thin films.[5] According to the European Medicines Company (EMA) and the Food and Drug Administration (FDA), a film that easily dissolves in the oral cavity is referred to as an orodispersible film or unquestionably soluble film.[3] Fast-acting oral films are typically incredibly thin (50–150 μm), about the thickness of a postage stamp, and they disintegrate in the mouth cavity in about a minute when they come into touch with saliva. This allows for immediate absorption and on-the-spot drug bioavailability.[8]

Drugs embedded in buccal adhesive films are quickly absorbed through the buccal mucosa, which then distributes the drug to the systemic circulation.[22] Similarly, wafer is commonly defined as paper-film polymeric films that are used as suppliers to pharmaceutical companies. This novel dosage form is swallowed; however it doesn't require water to be swallowed in order for the medication to be absorbed.[23] Buccal films, which are intended to remain at the cheek mucosa for a longer period of time, should no longer be confused with orodispersible films.[24] As a result, certain film genres must to be clearly visible in order to avoid potential misunderstandings.

III. ADVANTAGES OF THIN FILMS AS RISING DOSAGE FORM

Benefits over the usual dosage A thin film breaks down faster than other conventional dosage types.[9] When compared to commercially available oral rapid dissolving capsules that need specific packaging, film films are less friable and simpler to grip. In a similar vein, I think that a single dose of strip can travel without the extra package. It is critical to address the low stability of liquid dosage forms, especially aqueous formulations. In contrast to thin films, patients would need superior care, which includes precisely calculating the dosage and shaking the container before each use. Lower patient acceptability may also be caused by these reasons.[3]

Traditional ophthalmic drug administration methods, such as eye drops or solutions, are frequently employed; however, their capacity to offer prolonged duration of action and high ocular drug bioavailability is restricted. It may be possible to improve medication delivery to the attention by using ophthalmic thin films. Compared to transdermal patches, transdermal films have less of an impact on skin inflammation because they have less occlusive properties that allow water vapour to penetrate the skin more easily and leave the application site feeling less sticky.

Scientific Benefits

Because of its appealing form and ease of use, thin film is the treatment of choice for patients.[10] Moreover, oral dissolving film is very helpful for elderly, mental, and pediatric patients since it is easy to use and eliminates the risk of suffocation or choking, protecting the

patient's safety.[22] It was known that ophthalmic films lengthened a drug's retention period, which significantly accelerated the drug's absorption from the front of the eye. Additionally, because the polymeric thin films are easy to deliver and rarely spit up, they may be helpful for patients who are immobile and uncooperative.

IV. PRINCIPAL LIMITATIONS OF FILM FILMS

The low drug loading ability of a less potent agent administered at high doses occasionally restricts the use of film films.[10] Thin films typically exhibit hygroscopic properties. As such, special care needs to be taken to ensure their longer preservation.[4] It is extremely difficult to combine more than one medication at once in an oral film system since doing so slows down both the disintegration time and the dissolving charge of each medicine.

The challenge of achieving a high degree of precision regarding the amount of medicine in the character unit dose of the movie might lead to outcomes that are not repeatable, serious side effects, and treatment failure for the patient. The preparation for the oral film method tackles the problem of drying too slowly. Drying at room temperature is a one-day method that significantly reduces the cost of film production. It is no longer advised to dry thermolabile tablets in a hot air oven; thus, alternative drying techniques need to be looked into.

Polymers for Film Films

Polymers aid in the creation of film formulations, and a range of polymers can be employed to direct the process.[11] The polymers can be used alone or in combination with other polymers to obtain the desired film residences. The polymers that are used ought to be non-irritating, non-toxic, and free of any impurities that might leak out. Water-soluble polymers are used as film formers to produce films with the required mouth feel effects, a rapid disintegration rate, and the right amount of mechanical energy. In film education, polymers that are both natural and synthetic are utilized.

A list of typical polymers utilized in the creation of polymeric films is included in Desk 1, along with further details on each polymer's characteristics. The availability of several polymers makes it possible to impart unique properties inside the film films. For instance, various gelatins have varied molecular weights; as a result, smooth, visually appealing films will be produced using gelatin with a greater molecular weight. Pullulan is widely utilized to make thin films with strong mechanical properties, high solubility, and thermal stability across a broad range. The combination of chitosan and either low methoxy pectin (LMP) or high methoxy pectin (HMP) produced a film with remarkable mechanical electricity.

Because the film-forming polymers are hydrophilic, which promotes water retention, they generate thin films with low water vapor barriers, such as hydroxypropyl cellulose (HPC), methyl cellulose, and carboxymethyl cellulose (CMC).[12] In a single investigation, the outstanding hydroxypropyl methylcellulose (HPMC) grades Methocel E3, Methocel E5, and Methocel E15 top class LV were utilized as the fundamental film forming to create a fast-dissolving triclosan film. The finished result showed that Methocel E5 top rate LV at a concentration of 2.2% w/v may be used to generate films with exceptional film quality. In

vitro house time was nearly twice as lengthy for the film made with Carbopol® 934P and HPMC E15 as it was for the films made with the best HPMC E15.

The use of low-dextrose maltodextrins (MDX) as a film-forming polymer for the preparation of oral fast-dissolving films of the insoluble medication piroxicam was announced by Cilurzo et al. Despite the medication being loaded as a powder, which reduced the film's ductility, the resulting film had excellent flexibility, resilience to elongation, and quick disintegration. Additionally, oral dissolving films of synthetic granisetron HCl made with pullulan and HPMC demonstrated how increasing polymer concentration affected mechanical residences.

Now, pullulan at a concentration of forty–fifty five percent was unable to create films with the proper strength, and HPMC at a concentration of forty percent produced films that were challenging to peel. In a similar vein, the stickiness of the film increased when the HPMC concentration rose above 50%. Mucoadhesive films release medication into an organic substrate instantly and are flexible, film-based retentive dosage forms. They make it easier for users to stay longer on the application page, which prolongs the therapeutic effects. The majority of thin films with mucoadhesive properties are hydrophilic in nature, swell, and interact with mucin in a chain reaction.[11]

The most convincing mucoadhesion residences have been shown by chitosan, hyaluronan, cellulose derivatives, polyacrylates, alginate, gelatin, and pectin among the many polymers that have been studied.[13] Compared to non-ionic polymers, the cationic and anionic polymers enable a stronger contact with mucus. Anionic polymers are beautifully characterized by the presence of carboxyl and sulfate functional groups, which produce a bad charge at pH values greater than the polymer's pKa.

For instance, due to its ability to form bonds with mucin, polyacrylic acid (PAA) and sodium carboxymethyl cellulose (NaCMC) have remarkable mucoadhesive properties. Thiomers, or polymers with a thiol structure, are unique in that they can interact with mucin by forming disulfide bonds, which improves mucoadhesion. Many polymers can be employed in the "thiloation" process, which uses amide-coupling chemistry and aqueous solvent structures. Eudragit demonstrated encouraging mucoadhesive properties when employed either alone or in conjunction with several hydrophilic polymers. Films arranged according to propranolol HCl.

Table: Characteristics and Important Discoveries of Representative Polymers Utilized in the Creation of Film Formulations. [6, 11, 36]

Name of Polymers	Various Characteristics
(HPMC)	• A tasteless, odorless, creamy white powder • From 10,000 to 1,500,000 Mw This non-ionic polymer has mild mucoadhesive characteristics ranges from 3 to 100,000 mPa. Solutions remain stable between pH 3.0 and pH 11.0. • Capacity to create films at concentrations of 2-20% • Usually utilized to deliver the narcotic substance in a controlled or delayed manner

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	• Gradual or persistent drug release diffusion was observed after an initial burst of drug release.
(CMC)	• Easily distributed in water to create a colloidal or transparent solution 1% aqueous solution; η 5–13,000 mPa; high swelling qualities • Strong bioadhesive properties • Extended HPC and sodium alginate film residence times • The CMC that has been enzyme-modified exhibits good film-forming properties.
(HPC)	• Soluble in cold and hot polar organic solvents such as absolute ethanol, methanol, isopropyl alcohol and propylene glycol • Moderate mucoadhesive properties 5% (w/w) solution is typically used for film coating.
(PVP)	• High swelling qualities; • Non-ionic; • Wide range of solubility; • Used as a co-adjuvant to improve mucoadhesion. PVP can be blended with PVA and HPMC to improve its ability to form films.
(PVA)	• Water soluble synthetic polymer; • Non-ionic polymer; • Granular powder with a white to cream tint; • Mw 20,000–200,000; • Moderate mucoadhesive qualities • Extremely pliable films • Mostly utilized at concentrations of 3-5% in ophthalmic polymeric formulations. • Greater lengthening at break values
(PEO)	• Non-ionic polymer • High mucoadhesion with high molecular weight • By mixing low Mw PEO with a higher Mw PEO and/or with other materials, the tear resistance, dissolving rate, and adhesion tendencies of the film can be optimized. cellulose • Films that are easy to break and curl very little or not at all • Tasty mouthfeel without the production of sticky or extremely viscous gels
Pullulan	• Powder, white, tasteless, and odorless; Mw 8000–2,000,000 • Have more than 6% w/w of moisture Pullulan-HPMC films exhibit better mechanical and thermal qualities.
Pectin	• A mucilaginous, odorless, yellowish-white powder with a Mw of 30,000–100,000. • Water soluble yet insoluble in the majority of organic solvents; • High mucoadhesive qualities
Chitosan	• They were not very helpful for films that dissolve quickly.

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	• Brittle and lack a noticeable plastic deformation; • Good film-forming capacity at low temperatures
Sodium alginate	• Is a tasteless, odorless powder that is white or buff in color; it is a purified carbohydrate product made from brown seaweed using diluted alkali • Insoluble in acids and other organic solvents when the resulting solution's pH is less than 3.0
Carrageenan	• Iota, Kappa, and Lambda are the three structural types of this anionic polysaccharide, which vary in their rheology and solubility. • It can stabilize proteins and peptides by steric stabilization; • It works well with the majority of anionic and nonionic
Gelatin	• Can be used to create sterile sponge, ophthalmic film, and sterile film; it has excellent film-forming capabilities.

The mucoadhesive force of the film prepared using chitosan as the mucoadhesive polymer was three times lower than that of the plasticizer triethyl citrate and eudragit RS100. [11] Juliano and associates created buccoadhesive films with chitosan, HPMC, or alginate, either separately as an unmarried polymer or in combination with one or both of them. The main purpose of the films was to distribute the chlorhexidine diacetate in a regulated way. Since over 80% of the medication was released in less than 30 minutes, HPMC was unable to postpone the release of chlorhexidine any longer.However, when chlorhexidine was added to alginate and alginate/chitosan-based entire films, the amount of medicine that was released in thirty minutes was only thirty to thirty-five percent; for this reason, this polymeric device is useful for release of drug.

Polymers are known as excipients, which is not unusual, but they have become important when developing and constructing thin films. In order to maximize their use to increase a film film, knowledge about the homes of polymers as well as their chemistry, rheology, and physicochemical qualities seem to be emerging. At some stage in the development of polymeric thin films, the choice of an appropriate polymer can be critical, thus a number of aspects need to be taken into account in accordance with the specifications. As such, selecting the appropriate polymer is essential to producing a film with superior performance that guarantees high healing success.

V. METHODS FOR PREPARATIONS OF FILMS

The two methods most frequently employed for teaching film films are warm soften extrusion and solvent casting.[14] But inkjet printing, a ground-breaking method, has advanced in the last several years. Various methods employed in the production of polymeric films are outlined in the following element:

Solvent Casting

Solvent casting is one of the many film manufacturing procedures that is feasible, the most appropriate, and unquestionably the most generally used method, especially because of the genuine production system and inexpensive processing charge. Fig. 1 shows the process of creating film films using the solvent casting technique along with the appropriate control

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parameters at each stage. Because they have an impact on drying, the polymeric combination's rheological characteristics should be taken into account.

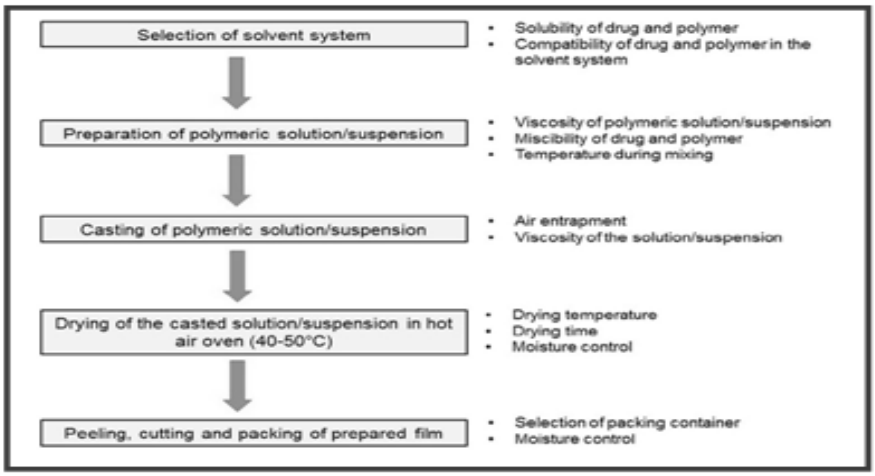

Figure 1: Solvent Casting Method for Thin Film Preparations

Thickness, the films' shape, and their consistent composition. To get a homogenous product, de-aeration is deemed required as the mixing procedure may unintentionally add air bubbles into the liquid.[15] Following the proper casting of the solution into the suitable substrate, they can be allowed to dry such that the solvent evaporates, leaving behind a polymeric film that contains a medication.[2] The film is reduced into an appropriate shape and length depending on the required dosage of the created strip once it has completely dried. In most cases, the strips are rolled and kept for a predetermined amount of time before being sliced; this is known as "rollstock" in the business world.

However, a film shouldn't be exposed for a lengthy amount of time because it is more prone to get damaged. It must be sliced and packaged as soon as possible after the coaching in order to preserve its equilibrium. A film produced via solventcasting has several advantages, including enhanced physical properties, easy and affordable manufacture, and exceptional thickness uniformity.However, there are a few problems with this approach. For instance, a polymeric film that was formed using the solvent casting technique became brittle after being stored, as evidenced by a drop in the percentage of elongation as a result of the solvent's evaporation or disappearance over time.[16]

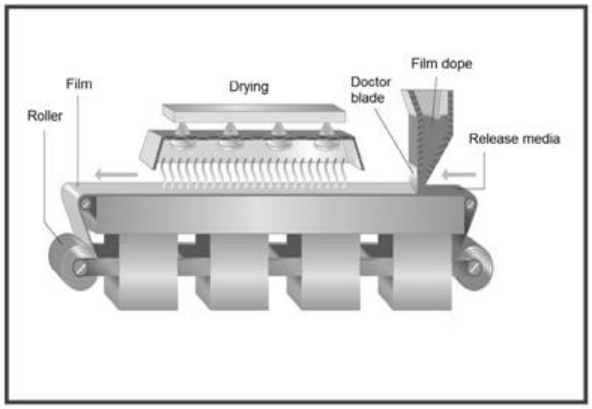

Figure 2: Commercial Manufacture of Film Based on Solvent-Casting [22]

One of the biggest obstacles in film production is moving from bench scale to production size. This is because a number of factors, including temperature, heating, and mixing speed, can vary greatly, making it difficult to produce films consistently on a commercial scale. Consequently, a significant amount of effort must be put into optimizing the number of variables, including as the drying time, the ultimate thickness of the dried strip, and the casting rate. These traits could also influence the production of movies on a commercial basis.[17] Fig. 2 depicts the equipment used for the large-scale manufacture of films primarily based on solvent casting process.

Hot-Melt Extrusion (HME)

HME is a flexible process that is used to make thin films as well as granules, capsules, and pellets,[18] It is a viable alternative to solvent casting for film guidance, especially where an organic solvent device is not required.[10] The majority of the literature, however, has recommended using warm-soften extrusion to produce polymeric thin films.[11] HME is a process that involves melting all of the ingredients to form a film from a mixture of polymers, drug material, and several excipients.[3] The films are then shrinking to a predetermined size and form.[6] Using this method, a molten mixture of medicinal ingredients is charged through a die-like aperture to create homogenous matrices.[11]

(1) feeding the additives through a hopper into the extruder; (2) blending, mixing, and kneading; (3) feeding the blended and melted mass into the die; and (4) extruding the mass through the die and then processing it downstream.

The hopper, extruder, film die, and curler comprise the apparatus for the HME method shown in Fig. 3. Within a stationary cylindrical barrel, one or more co-or counter-rotating screws make up the extruder. To reduce the molten cloth's house time, the barrel is frequently made in pieces. The barrel's sectioned portion is fastened together by both bolts and clamps.

One of HME's benefits is that it creates a medication in a stable dispersion or solution, which could increase the solubility of capsules with low solubility.[19] However, as the temperature drops, there may be a significant possibility of API recrystallization in the polymer mixture at higher temperatures. You can avoid this problem by using a more viscous polymeric compound or increasing the amount of plasticizer. The "Die swell phenomenon," which refers to a boom that occurs inside the film's move phase following its ejection from the die and is caused by the viscoelastic properties of polymers, is the other challenge associated with HME.

This is because the polymer can sustain high shear force during extrusion and high strength kneading. This problem can be avoided by reducing the screw's speed or by slowly mixing molten material for an extended period of time as opposed to using severe shear kneading for a short period of time.[20] This method, in contrast to solvent casting, eliminates the need for natural solvent, making them environmentally benign.[2]

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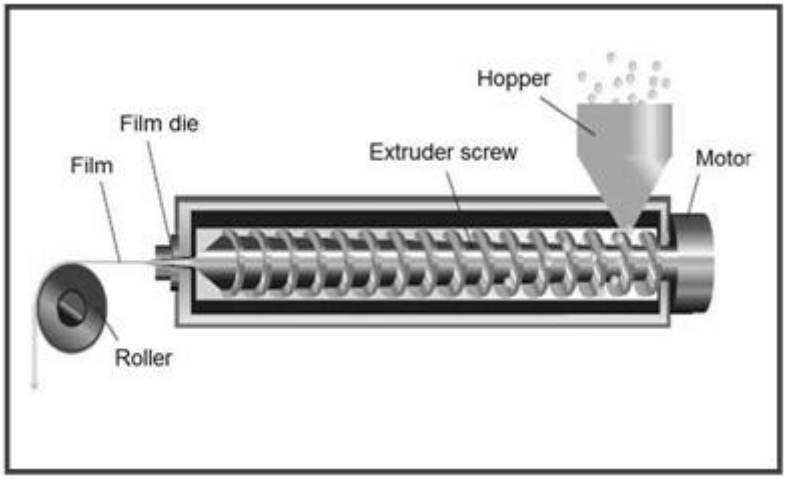

Figure 3: Hot-melt extrusion method for film preparation [22]

Printing Technology

Polymeric film could be produced using innovative methods in addition to 3-D printing. It might serve as a framework for creating a dose form that the affected character can employ. This may help pharmacies and the pharmaceutical industry meet the need for tailored medications in the future.[23] Because printing technologies are flexible and affordable, they are becoming more and more popular. From the perspective of the pharmaceutical industry, printing technologies are typically used for determining or labeling pharmaceutical dosage documentation, especially to optimize the product for easy identification and to stop the creation of counterfeit goods.

This method has, nonetheless, just been used to prescription dosage reporting for drug loading.[3] One example is the production of precisely dosed pharmaceutical components using drug-loaded inks deposited in consumer inkjet printers that are readily available off-the-shelf. Furthermore, a fantastic fusion of inkjet and flexographic technology has been employed.[24] Inkjet printing was used to print API on certain substrates, while flexographic printing was employed to cover the drug-loaded substrate with a polymeric thin film.[25] Medication components can be loaded onto transdermal patches using either screen printing or pad printing; pad printing has limitations because of its sluggish manufacturing rate.

In recent times, inkjet printing has gained popularity as a dependable and precise way to fabricate film components for dosage forms of potent medications that are delivered at low dosages.[24] To complete the preparation of several layers, a second printing layer can be layered on top of the first, with or without an intermediate base film layer. Furthermore, the broadcast layer would be shielded by a 2D base film layer. This might lead to altered drug release patterns and protect the ink layer from mechanical strain or separation during processing like packing or shrinking.[25] When used, each of them contributes to the production of a movie with more consistent drug dose and distribution.

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The amount and characteristics of the processed drug components naturally induce coating mass homes, such as viscosity or density, which account for the dosing accuracy and equal distribution of the drug materials within the films. It can be quite difficult to ensure the same dosage precision inside the man or woman devices when using the old approach of film guidance.[3] In summary, printing a medication on a dosage form is a powerful tool that can produce dosage forms with remarkable balance, velocity-capability, and uniformity. It is the modern solution for film guiding. The following lists printing technologies that have been applied to the production of polymeric film films.

Inkjet Printing

Inkjet printing is a more modern form of advanced printing that stands out for its precision, repeatability, versatility, and reasonably priced approach of depositing tiny quantities of solution in films. Inkjet printing offers an opportunity to make bespoke pharmaceuticals and can be quite beneficial for the coaching of low dosage medications.[26] The two primary subsets of the inkjet era are continuous inkjet printing (CIP) and drop on demand (DoD) printing. Both print and generate the droplets in a way that is remarkable. Through a nozzle aperture within the CIP container, a liquid is periodically discharged, fragmenting into a stream of droplets below the surface anxiety pressure.

Utilizing an electric price on a few of the drops that divert the stream away from the main axis beneath an electrostatic discipline makes this feasible. However, in drop-on-demand printing, the liquid is only ejected from the print head when a drop is needed. The creation of a single drop occurs quickly beneath the trigger sign's reaction. A DoD printhead has many nozzles (ranging from one hundred to a thousand, while a professional printhead might also have an unmarried nozzle). The kinetic energy of the drops produced by the source positioned inside the printhead adjacent to each nozzle causes the drop ejection.[27]

The density or viscosity of the ink (drug substance answer or suspension) determines the printability properties, which in turn impact the drug substance's uniform distribution and dosage precision inside the film.[3] Janßen et al. showed how to apply a modest quantity of salbutamol sulfate using a standard computer printer on commercially available films that are primarily composed of starch.[10] But although inkjet printing is unsuited for high volume commercial production, flexographic printing appears to be more suited for business education.

Flexographic Printing Era (FPT)

FPT is a method that carefully transfers an active pharmaceutical component into film films using touch printing.[10] Figure 4 shows the flexographic printing system, which is a rotating printing mechanism. An anilox curler is used to measure ink, such as drug material solution and suspension, before it is transferred to a printing cylinder, which prints the film after the daughter roll has been unwound.[3] For items that are sensitive to heat, including proteins and peptides, it is beneficial. If the film technique's combining and drying are finished before the medication is administered, the issues related to API lack of leisure can be avoided. Given that 530 oral films can be produced each minute at a low cost and with a high production efficiency, this process can be used.

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When printing medicinal solutions, flexographic printing exhibited no influence on the mechanical characteristics of polymeric thin films.[28] Janßen et al. conducted a research and found that tadalafil and rasagiline mesylate solution could be discharged onto hydroxypropyl methylcellulose sheets using flexographic printing. It is believed that hydroxypropyl cellulose synthesis reduces the crystallization of medications after printing. However, the primary drawbacks of flexography are that it is not appropriate for large-scale manufacturing because to its extremely poor resolution, high risk of infection, and need for print curler preparation.[10]

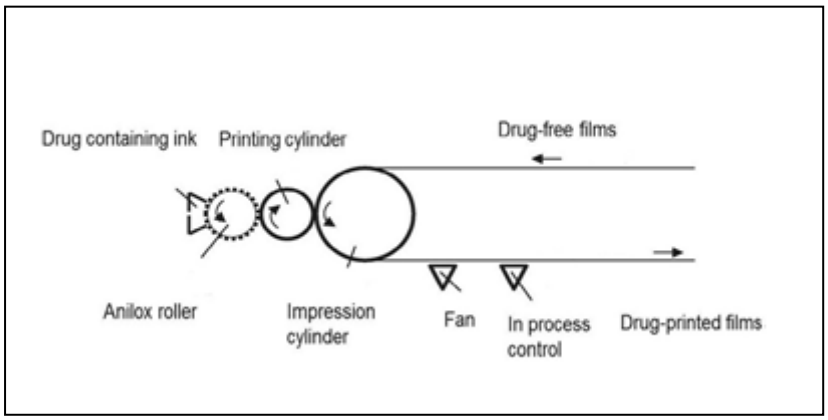

Figure 4: Overview of flexography technology[46]

Regarding Quality of Thin Films

A film must possess the necessary physicochemical balance, elasticity, softness, and flexibility to be perceived as ideal thin film. To ensure the film's effective performance, the majority of these criteria must be properly taken into account as it is being grown. The pre-determined requirement of characterizing a film includes evaluating its mechanical strength, hydration, in vitro release, and surface shape, among other attributes. The next section lists the various key quality factors that have an impact on film theaters and the commonly used in vitro techniques for characterizing films.

Thickness and Weight Variation

The thickness measurement is important because it immediately connects to the amount of drug in the film. Furthermore, a certain thickness is required for handling films comfortably. Buccal films, for example, need to be sufficiently thick, ideally between fifty and one thousand micrometers.[12] The thickness of the manufactured film films is often measured using a Vernier caliper, an electronic digital micrometer, a screw gauge, or pictures from scanning electron microscopy (SEM).[29] It is believed that the amount of plasticizer in the formulation somewhat increases the film thickness.[30] by adding m (Batch), the total mass of the batch, m (API/film), the quantity of drug per film, ρ (Batch), the density of the component, and m(API).

In this case, mass (m), density (ρ), and area (A) are expressed in g, g/cm3, and cm2, respectively. Active pharmaceutical ingredient is referred to as API. The load variation is often computed to ensure that each film carries the typical dosage of a medication without a

substantial deviation. It is calculated by weighing each unique film and, in turn, the average weights of films that are identical. Each patch's weight is split by the film's overall weight. The mean ± SD values for every formulation are calculated. There is a good chance that the medication content won't be consistent if there is a large variance in weight, which indicates that the technique employed was unsuccessful.[12]

VI. PHYSICAL AND MECHANICAL PARAMETERS

Polymeric films must be sufficiently eager to be readily ejected from the pouch, coiled up after casting, and peeled off the release lining. They shouldn't be too flexible, either, since extra elongation during packing and reduction might alter the film's quantity and result in uneven API amounts according to the film.[32] Film mechanical qualities may be described using tensile power, tear resistance, percentage elongations, and Young's modulus. [33] Hard and strong polymers are known to have high tensile strength, excessive elongation at breakage, and high Young's modulus, whereas soft and malleable polymers are known to have low tensile strength, low elongation at breakage, and low Young's modulus.[11]

Moreover, the mechanical characteristics of films are influenced by the formulation and production processes. A few well-known film characteristics that were observed using strain—pressure curves are shown in Figure 5. The attention to detail and styles of the polymers are significantly responsible for the film's exceptional mechanical strength and integrity.[34] In a similar vein, the morphological structure of the film may also alter the mechanical strength, for instance by crystal boom.[64] For this reason, controlling the mechanical strength of the film requires careful consideration of a number of factors, such as the film-forming agent, the production method, the thickness of the film, and the kind and quantity of API it contains. Enhancement can be achieved by combining and cross-linking additional or mixed polymers.

After cross-linking, the film maintains its integrity and appearance, albeit the film floor may become harder. This conclusion is supported by the fact that PVA–NaCMC films have higher mechanical residences than PVA or NaCMC films made alone. The PVA-NaCMC film was found to have a tensile strength that was thirteen to seventeen times greater than films made with the synthetic polymer N-vinylpyrrolidone.

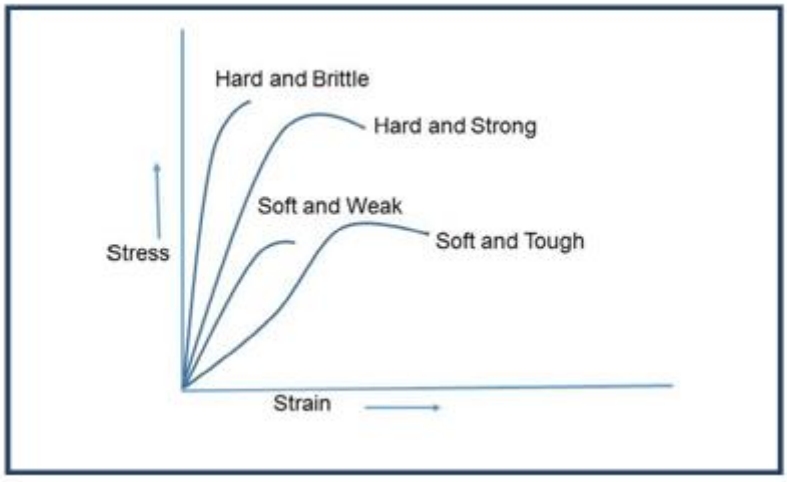

Figure 5: Stress–strain curves from polymeric thin films [11]

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The application of plasticizer can help dissolve the stiffness of the film structure and alleviate brittleness by lowering intermolecular tensions. The plasticizers propylene glycol, glycerol, sorbitol, and polyethylene glycol are usually used in the greatest concentrations. However, adding too much plasticizer might lower the adhesive energy of films by overhydrating the film formulations.[36] For example, glycerine breaks the link between every man and woman strand of polymer by intercalating itself between them. The tertiary structure of the polymers becomes more flexible and porous. Because of this, the plasticized polymer deforms at a lower tensile force than a polymer without plasticizer.[37] The most popular method for determining a polymeric film's mechanical strength is to employ a texture analyzer, as demonstrated in the majority of literary works.

The device begins measuring the force and displacement of the probe as soon as it makes contact with the sample. A person pattern holder for small-sized film sample useful resource size is present (Fig. 6). Films are secured between two plates using screws of the appropriate diameter inserted into a cylindrical hole. The plate is stabilized to prevent movement by pins that are positioned precisely beneath the punch. By making adjustments, the probe may be advanced to the required running velocity. The measurement changes as soon as the probe touches the sample floor, which initiates pressure.

Until the film splits, the probe continues to advance at the same, steady pace. Recording the applied pressure, displacement (penetration depth), and surrounding temperature and relative humidity is crucial at the end. [38] During the process of using a texture analyzer to measure mechanical energy, it was discovered that the contact time, touch pressure, and rate of probe withdrawal all had a substantial effect on the experimental outcome.[39] The tensile strength is determined using several metrics, such as younger's modulus, elongation at ruin, % elongation, and folding staying power.

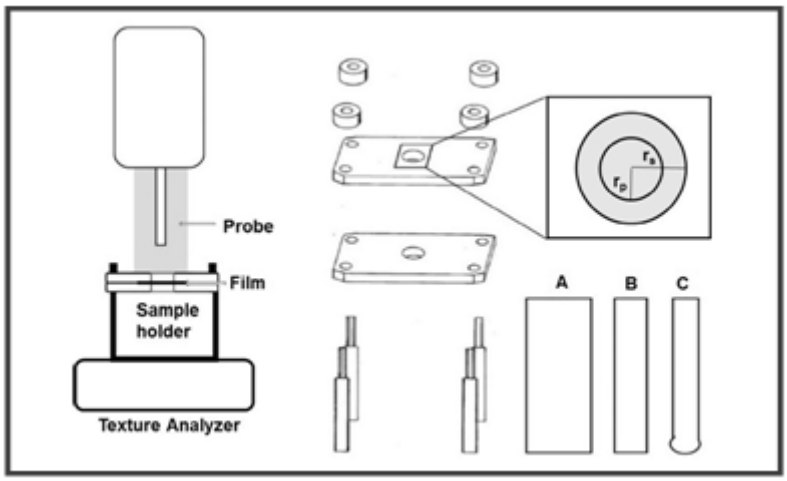

Figure 6: The sample holder for the film preparation (right) and the experimental setup (left) are shown, with rs denoting the sample radius and rp denoting the probe radius. The bottom right corner displays the geometry of the spherical probe C and the cylindrical probes A and B. [47]

Folding Persistence

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When considering that the films may be administered without breaking, thin film power is essential. One can gauge the polymeric film's power by looking at how patiently it folds. The film is folded repeatedly at an angle of 180° from the plane in the same spot until it breaks, which is how the folding endurance is calculated. A film with a folding patience price of three hundred or more is regarded as having extraordinary flexibility. [40]

Percent Elongation and Elongation at Smash

One type of deformation known as elongation is the straightforward change in shape that any object experiences when subjected to extreme strain. Put another way, sample deformation occurs when the pattern is subjected to tensile pressure, which causes the pattern to stretch or elongate.[17] The size of elongation is typically carried out to predict the polymer's ductility. With the aid of a texture analyzer, elastic elongation or elongation at wreck of a material can be determined. All elastomer types exhibit the phenomenon of elastic elongation. The percentage elongation shows the amount of fabric that can be stretched before breaking, whereas the elongation at ruin describes the amount of time that the film can be extended after being torn (or broken) by the applied probe.

Sample elongations become more significant as the amount of pressure increases because stress is generated when pressure is applied to a sample. When the sample achieves a positive value, it breaks; this breakage factor is known as the percentage elongation spoil. where b is the penetration intensity/vertical displacement through the probe, r is the radius of the probe, and a' is the length of the film that the probe has no longer pierced. An is the movie's starting runtime in the sample keeping.

$$\% \text{ elongation} = \frac{Increase\ \ lengt\,h\ of film}{Initial\ \ lengt\,h\ of\ film} * 100$$

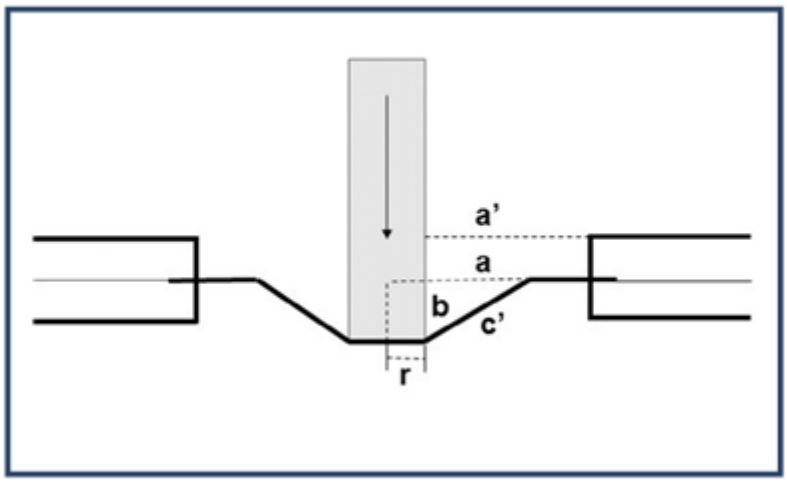

Figure 7: Utilizing a texture analyzer, determine the percentage elongation of thin films by taking the following values: a = initial length of the film in the sample holder opening; a' = initial length − radius of probe; b = probe displacement; c' + r = length after strain; c' = length of a' after strain; and r = probe radius. [47]

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Younger's Modulus

The films' stiffness or elasticity is shown by their elastic modulus, also known as Younger's modulus. This indicates that the films are resistant to deformation, which may be determined by charting the stress-strain curve, the slope of which indicates the tensile modulus—the higher the slope, the higher the tensile modulus. Conversely, the modest slope technique results in reduced deformation and tensile modulus.[41] To be honest, the only thing that is challenging and brittle with little elongation is a film that exhibits higher tensile power and greater Young's modulus values.

The strain strain curve provides the slope for the Young's modulus, which can be calculated using a texture analyzer. The following system can be used to determine Young's modulus, which is defined as the ratio of applied pressure over strain inside the elastic deformation region: a variety of crosshead velocity may be acquired through converting the speed of the motor of the feel analyser.[15]

Tear Resistance

Tear resistance is the ability of the film's components to withstand a rupture. The amount of tear resistance is achieved by subjecting the film to a continuous deformation rate. Newtons or pounds-per-pressure are used to express the maximum force or strain required to rip the film.[17] The location of the plot in a stress stress curve indicates the tear resistance.

Moisture Content

The quantity of moisture in the film can be important since it affects the mechanical strength, adhesive qualities, and friability of the film.[42] Raising the water stage is caused by a number of reasons, including the hygroscopicity of API, polymers, the solvent system used to dissolve the polymeric mixture, and production procedures. The moisture content of the film is often determined using a range of techniques, including weighing techniques and Karl Fischer titration. In the weighing process, preweighed films—also referred to as preliminary weight—are heated to a temperature of between 100 and 120 °C until they reach their usual weight. Eventually, the last dried sample load is removed.

Swelling

This is often where swelling homes of films are discovered since the polymers used to make them are hydrophilic. Polymer swelling is widely acknowledged to be a crucial step required for bioadhesion.[43] The diploma and swelling charge often play a significant part in controlling the drug release. These measurements can therefore be used as an indicator for mucoadhesive or bioadhesive capabilities as well as pharmaceutical launch characteristics. Testing for swelling is done up until the polymer hydration threshold.[44] Different degrees of swelling are experienced by hydrophilic polymers with distinctive systems based on molecular motion.

As the range of hydrogen bonds and the electrical charge between the polymers expand, water debris steadily diffuses into the hydrated matrix. Panomsuk et al.'s assertion that mannitol added to the methylcellulose matrix reduces the membrane's swelling index

was validated in this way.The tablets' and the polymeric matrix's formation of hydrogen bonds will cause this to happen. Measuring the swelling or degree of hydration of the polymeric film is an essential step in providing valuable information on the mucoadhesive potential. The hydration of the polymers is, as we all know, the cause of the rest and interpenetration of the polymeric chain; nevertheless, excessive hydration decreases the mucoadhesion residences by causing the creation of slippery gum.

The ratio of hydration is used to calculate the swelling residences, or water absorption capacity, of films. For example, the film piece is weighed (W1) and immersed in physiological fluid simulation for a predefined duration. Following the set amount of time, the pattern is removed, cleaned to remove any residual water from the floor, and weighed (W2). The following system, which is given in percentage, is used to finish the calculation.

Drug Release Profiles

To an incredible extent, the release kinetics of pharmaceuticals from the polymer matrix is principally dependent on the physicochemical properties of the substances used in addition to the morphology of the machine.[36]Variations in pH or temperature can cause polymer erosion or dissolution costs to increase or decrease. Drug diffusion results from the polymeric film swelling when it comes into contact with biological fluids because the polymer chain relaxes. The drug release is directly correlated with the polymer's form; for instance, linear amorphous polymers dissolve far more quickly than move-connected or partially crystalline polymers. According to a plethora of study, the film's deterioration has a significant impact on the drug's release.

The medication needs to be released from the transportation systems at its most effective charge in order for it to pass through the organic membrane. Evaluating the drug release from the film is crucial because it's the first step in the absorption process that determines the cost. Films and/or medications that dissolve are categorized with equipment that is approved for various levels of strict dose regulation. Within the literature, many authors have performed some innovation at the dissolution equipment, even as others have hired Franz diffusion cells (FDC) for testing the drug launch from the polymeric films.[12] The location of the samples is a major obstacle to film in dissolution testing.

A number of techniques have been used, wherein the film is attached to the stirring detail or the inside facet of the glass vessels using an adhesive tape.[24] Using a JP XIII dissolving apparatus at 37 ± 0.1 °C, Okamoto et al. performed a dissolution study on lidocaine film for buccal administration. A film was cut precisely into a circle with a one centimeter area, and double adhesive tape was used to attach it to a three centimeter diameter weight. The weighted film was then placed, as illustrated in fig., with the film dosage form facing upwards, into a tumbler container that held 500 ml of artificial saliva.

Surface Morphology

The film's shape needs to seem continuous and homogenous in order to guarantee that the medication is dispersed evenly throughout the polymeric mixture at every place. Because of the intermolecular and convective interactions that cause the surface to wrinkle, films may self-aggregate after they dry. Moreover, a hard floor may form inside the films as a result of the drug's interactions with polymers and crystalline structure. In order to ensure that drugs

are distributed uniformly and that there is no interaction with the polymers inside the film method, it is crucial to examine the surface morphology and texture. A number of floor characteristics, including thickness, drug distribution (spread or aggregated), and surface texture (smooth or rough) of the film, may be identified using light and scanning electron microscopy.

Packaging of Film Films

Packaging is crucial for maintaining the stability of film compositions and for ensuring mechanical safety. It serves as a barrier against oxygen, light, and moisture. While certain options exist for the packaging of polymeric thin films, not all of them are strong enough to maintain the product's physical properties and integrity. Since it shields the film from moisture and mild deterioration, aluminum foils are most frequently used and thought to be the best material for film packaging. If tamper-proof packaging is required, lidding foil has also been rented. To obtain a precise hermetic seal between the top and lower percent foils, films are sealed using several songs.[17]

Synthetic film can be packaged in foil, paper, or plastic pouches, which is an economical and hygienic solution that enables the flexible pouch to be formed in a clean, vertical or horizontal manner as the product is being filled.[4] These days, the strips are available in blister packs of two units as well as single dose sachets. Pfizer Customer Healthcare introduced a single dose sachet called PocketpaksTM for cold mint Listerine. In addition, a tear notch, slit, or reduce-off is fabricated to guarantee that the customer may easily peel off the PC. This approach is computer-pushed and automatic.[17]

VII. ROUTES FOR THE ADMINISTRATION OF FILM FILMS

Oral Route

The development of polymeric films has made it feasible to increase patient adherence to pharmacological therapy and drug bioavailability when taking medications orally, particularly sublingually and buccally. Because of its morphological and physiological characteristics, such as smooth muscle mass with high vascular perfusion, smooth accessibility, and bypassing first pass metabolism, the buccal mucosa is a favorable route for drug delivery. The oral cavity is made up of the tongue, lips, cheeks, hard palate, sensitive palate, and floor of the mouth.[2] Fig. 9 displays the common webpage for managing films to the buccal and sublingual mucosa. Compared to other mucosa, the buccal and sublingual routes offer higher drug permeability.

Ocular Route

Over 90% of ocular formulations on the market come in the form of answers or suspensions; nevertheless, this conventional dose form falls short of achieving meaningful therapeutic results. The goal of the typical eye drop application is to promote healing. Pulsed management and noncompliance from the affected person are the usual outcomes of this. Furthermore, the topically carried out medications to the eye generally enter the systemic stream thru the nasolacrimal duct machine, which probably purpose aspect consequences and

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systemic toxicity as well. The production of ophthalmic film is becoming well-known these days with the goal of improving ocular bioavailability and overcoming the constraints of ocular drug transport. Better healing outcomes, a significant decrease in systemic adverse effects, and a reduction in dosage frequency are all brought about by ophthalmic films.

Transdermal Route

The widely used transdermal dosage form can be replaced by drug-loaded transdermal films. There are several established sustained or controlled transport designs that dissolve or disseminate a drug inside the films. The film-forming process has been used to provide transdermal distribution of steroidal hormones, analgesics, local anesthetics, and antiemetic drugs for systemic effects. Because many factors affect a drug's bioavailability, such as molecular length, polarity, pH, country of skin hydration, subcutaneous drug reservoir, and drug metabolism through pores and skin vegetation, only a limited number of medications are being developed for transdermal delivery of films.

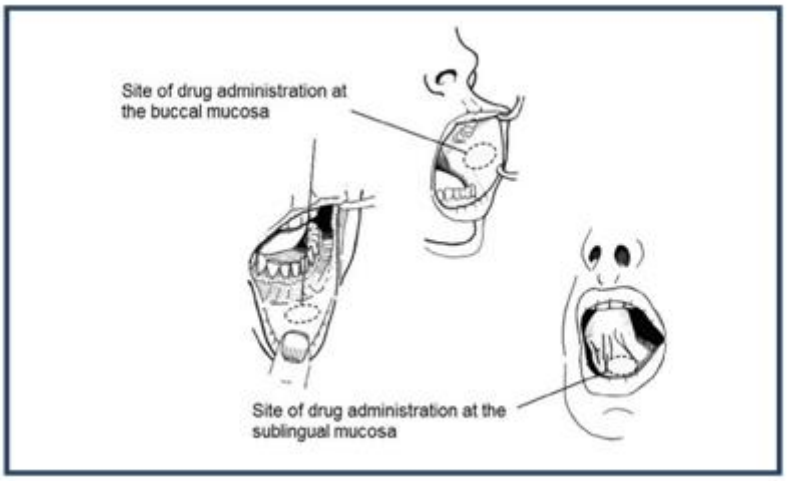

Figure 8: site for application of film [48]

VIII. CONCLUSION

The drug mix used in several movies has grown in popularity in recent years. The pain associated with administration, lower bioavailability, and patient non-compliance with current dose forms have all led to the creation of novel polymeric film films as a drug delivery platform. Established and up-and-coming pharmaceutical businesses are closely monitoring this medication delivery method. The firms aim to offer a broad range of thin films for oral, sublingual, ophthalmic, buccal, and transdermal routes. Therefore, in order to overcome the constraints imposed by the present dosage bureaucracy and provide an opportunity to standardize dose documentation, polymeric film films are projected to set themselves apart as a dosage form.

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