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3 **Thin films as an emerging platform for drug delivery**

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27   **Graphical abstract**

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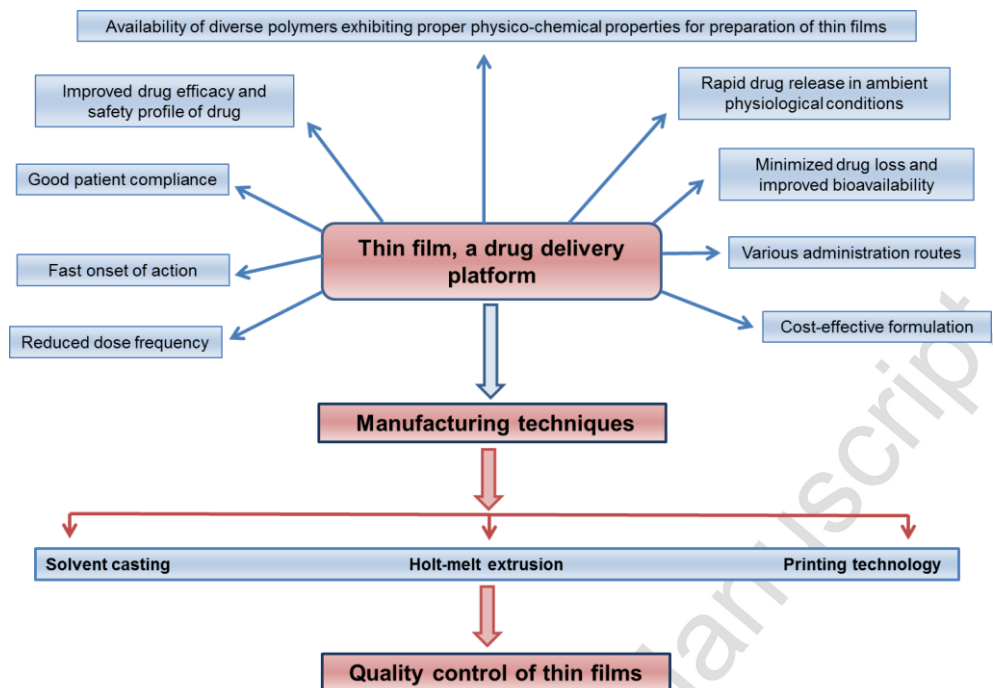
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31   This review provides an overview of critical factors, characterization methods, and quality
32   specifications for development of thin film formulations for drug delivery along with the
33   recent trends and future perspectives.

34

35   **Abstract**

36

37   Pharmaceutical scientists throughout the world are trying to explore thin films as a novel

38   drug delivery tool. Thin films have been identified as an alternative approach to conventional

39   dosage forms. The thin films are considered to be convenient to swallow, self-administrable,

40   and fast dissolving dosage form; all of which makes it as a versatile platform for drug

41   delivery. This delivery system has been used for both systemic and local action *via* several

42   routes such as oral, buccal, sublingual, ocular, and transdermal routes. The design of efficient

43   thin films requires a comprehensive knowledge of the pharmacological and pharmaceutical

44   properties of drugs and polymers along with an appropriate selection of manufacturing

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45 processes. Therefore, the aim of this review is to provide an overview of the critical factors

46 affecting the formulation of thin films including the physico-chemical properties of polymers

47 and drugs, anatomical and physiological constraints, as well as the characterization methods

48 and quality specifications to circumvent the difficulties associated with formulation design. It

49 also highlights the recent trends and perspectives to develop thin film products by various

50 companies.

51

52 **Keywords:** Thin film, Film-forming polymer, Mechanical properties, Manufacturing,

53 Characterization

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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

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88 fascinated by the appealing features of thin films and as a result, they have already patented

89 various technologies for producing thin films [17].

90   Currently, a significant amount of original works and patents can be found in literature,

91 but, still there is a need for extensive studies to optimize the performance of thin films

92 accurately. The lack of appropriate guidance for the manufacture, characterization and quality

93 control of the thin films has sought the need of adequate studies in this area from the

94 pharmaceutical viewpoint. Therefore, this paper will contribute to give insights on

95 understanding the critical quality attributes and characterization methods with the aim to

96 enhance the performance of thin films.

97

98 **2. Types of thin films**

99

100   Thin film is not a recent formulation, and it was first introduced in late 1970 to overcome

101 swallowing difficulties exhibited by tablets and capsules [15]. Various names of thin films

102 are appeared such as oral film (oral thin film), oral soluble film, wafer, oral strip,

103 orodispersible film (ODF), buccal film, mucoadhesive film, ophthalmic film, and

104 transmucosal film. While several films are designed to be dissolved quickly in the oral cavity

105 for the absorption of a drug in the gastrointestinal cavity (oral and oral soluble or,

106 orodispersible films), some are prepared to deliver a drug at the site of administration (e.g.,

107 buccal, sublingual and ophthalmic thin films). Drugs with high mucosal permeability have

108 been known to be suitable for buccal and sublingual delivery with films [18]. Likewise,

109 ophthalmic thin films are generally applied to treat diseases of the anterior segment such as

110 conjunctivitis, glaucoma and chronic dry eye syndromes [5, 19].

111   A film that readily dissolves in the oral cavity is generally termed as orodispersible film

112 according to European Medicines Agency (EMA) or simply soluble film according to FDA

113 [3]. Usually, fast dissolving oral films are ultra-thin film (50-150 μm) having size of postage

114 stamp, which dissolves within a min in the oral cavity after being in contact with the saliva

115 resulting in quick absorption and instant bioavailability of the drugs [20, 21]. Drugs loaded in

116 buccal adhesive films are absorbed directly *via* buccal mucosa, which delivers the drug to the

117 systemic circulation after their absorption [22]. Likewise, wafer is frequently mentioned as

118 paper-thin polymeric films employed as carriers for pharmaceutical agents. This innovative

119 dosage form is taken orally but does not require water to swallow for the absorption of a drug

120 [23]. Orodispersible films should not be misunderstood with buccal films designed for

5

121 staying longer on the cheek mucosa [24]. Therefore, different types of films should be

122 distinguished accurately to prevent possible misinterpretations.

123

124 **3. Advantages of thin films as an emerging dosage form**

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126 *3.1. Advantages over conventional dosage forms*

127

128 A thin film dissolves rapidly than other conventional dosage forms [25]. Thin films are less

129 friable and easy to carry dosage form compared to commercialized orally fast disintegrating

130 tablets, which need special packing. Likewise, a single dose of strip can be carried

131 individually without requiring the secondary container [26, 27]. It is very important to

132 address the poor stability of liquid dosage forms, especially the aqueous formulations. Unlike

133 the thin films, there is a need of great care during accurate measurement of the amount and

134 shaking the bottle every time before administration may contribute to less acceptance by the

135 patients [3]. Conventional ophthalmic drug delivery systems such as eye drops or solutions

136 are commonly used but they are limited in their ability to provide high ocular drug

137 bioavailability and sustained duration of action [28]. Ophthalmic thin films can be used to

138 improve the drug delivery to the eye. In contrast to transdermal patch, the transdermal film is

139 less associated with skin irritation due to less occlusive properties that improve the water

140 vapour permeation through the skin and do not leave sticky sensation on the site of

141 application [29, 30].

142

143 *3.2. Clinical advantages*

144

145 Patients show preference towards thin film due to its appellative form and ease of

146 administration [17]. Furthermore, oral dissolving film is extensively useful for pediatric,

147 geriatric, and psychiatric patients since it is easy to administer and avoid the risk of choking

148 or suffocation, thus ensuring patient safety [22]. Ophthalmic films have known to enhance

149 the retention time of a drug and thereby, the absorption of the drug was greatly improved

150 from the anterior segment of the eye [31]. Moreover, the polymeric thin films can also be

151 beneficial for bedridden and non-cooperative patients as they can be administered easily and

152 hardly spit out. A thin film is useful in cases where a rapid onset of action is required such as

153 in motion sickness, sudden episodes of allergic attack or coughing, bronchitis or asthma [22].

154

6

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4. Major limitations of thin films

157

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 decrease 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].

170

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5. Polymers for the preparation of thin films

173

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

7

188 mechanical strength. The film forming polymers such as hydroxypropyl cellulose (HPC),

189 methyl cellulose, and CMC produce a thin film with less water vapour barrier due to

190 hydrophilic nature which aids in water retention [15].

191 In one study, a fast-dissolving film of triclosan was prepared using different grades of

192 HPMC named as Methocel E3, Methocel E5, and Methocel E15 Premium LV as a primary

193 film former. The result demonstrated that Methocel E5 Premium LV at the concentration of

194 2.2% w/v produced films with excellent film properties [37]. The *in vitro* residence time of

195 the film made from Carbopol® 934P and HPMC E15 was almost double than the films

196 containing only HPMC E15. Additionally, it was observed that the combined polymers were

197 more resistance to breakage [11]. Cilurzo et al. (2008) reported the use of maltodextrins

198 (MDX) with low dextrose content as a film forming polymer for the preparation of oral fast-

199 dissolving films of an insoluble drug, piroxicam. Despite the decrease in film ductility due to

200 the loading of the drug as a powder, the produced film exhibited satisfactory flexibility and

201 resistance to elongation along with rapid dissolution [38]. Similarly, oral dissolving films of

202 granisetron HCl manufactured using HPMC and pullulan illustrated the effect of increasing

203 polymer concentration on mechanical properties and physical properties of films. Pullulan

204 with 40-45% concentration was not able to produce films with good strength whereas the

205 HPMC used in 40% concentration yielded the film which was difficult to peel. Likewise, the

206 film stickiness increased when the concentration of HPMC was beyond 50% [39].

207 Mucoadhesive films are thin and flexible retentive dosage forms, and release drug directly

208 into a biological substrate. They facilitate in extending residence time at the application site

209 leading to prolonged therapeutic effects [40]. Majority of the thin film having mucoadhesive

210 properties are hydrophilic in nature that undergoes swelling and form a chain interaction with

211 the mucin [11]. Among the several studied polymers, the most compelling mucoadhesion

212 properties are exhibited by chitosan, hyaluronan, cellulose derivatives, polyacrylates,

213 alginate, gelatin and pectin [41]. Compared with non-ionic polymers, the cationic and anionic

214 polymers facilitate strong interaction with mucus [42]. Anionic polymers are well-

215 characterized due to the existence of carboxyl and sulfate functional groups, which create the

216 negative charge at pH values surpassing the pKa of the polymer. As an example, sodium

217 carboxymethyl cellulose (NaCMC), and polyacrylic acid (PAA) exhibit excellent

218 mucoadhesive properties because of bond formation with the mucin [43]. Thiomers i.e.

219 polymer containing thiol group stand out to enhance mucoadhesion because they are able to

220 interact with the mucin through the formation of disulphide linkages. The process of

221 'thiloation' is possible with many polymers, using amide-coupling chemistry, where the

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222 aqueous solvent systems are used [44]. Eudragit displayed promising mucoadhesive
223 properties when used alone or in combination with other hydrophilic polymers. Films,
224 prepared from the propranolol HCl, Eudragit RS100, and triethyl citrate (plasticizer),
225 demonstrated mucoadhesive force three times greater than the film prepared with chitosan as
226 the mucoadhesive polymer [11]. Juliano et al. (2008) prepared a buccoadhesive films
227 constituting alginate and/or HPMC and/or chitosan either as a single polymer or in a
228 combination of two. Basically, they aimed the films to release the chlorhexidine diacetate in a
229 controlled manner. HPMC was not able to prolong the chlorhexidine release as more than
230 80% of the drug was released within only 30 min. However, chlorohexidine incorporated in
231 alginate and alginate/chitosan-based films showed that only 30-35% of the drug was released
232 in 30 min; hence, this polymeric system is beneficial for prolonged drug release [45].

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

241

242 **6. Technologies for manufacturing thin films**

243

244 The most commonly used techniques for the preparation of thin films are solvent casting
245 [46, 47] and hot melt extrusion [38, 48]. However, an innovative technique like inkjet
246 printing [49] has evolved in the past few years. Various methods that have been employed for
247 polymeric thin film manufacturing are described below in detail:

248

249 *6.1. Solvent casting*

250

251 Among several techniques of film manufacturing, solvent casting is feasible, preferable
252 and undoubtedly widely used method mainly due to the straightforward manufacturing
253 process and low cost of processing. The manufacturing procedure of thin films with the
254 solvent casting method along with the quality control parameters in each step is illustrated in

9

255 **Fig. 1.** The rheological properties of the polymeric mixture should be taken into account
256 since they affect the drying rate, the film thickness, the morphology as well the content
257 uniformity of the films [26]. The mixing process could introduce the air bubbles into the
258 liquid inadvertently; therefore, de-aeration is a pre-requisite to obtain a homogeneous product
259 [17]. After casting the solution into a suitable substrate, they are left for drying to allow the
260 solvent to evaporate that just leaves a polymeric film with a drug on it [2].

261 After the complete drying of the film, it is cut into suitable shape and size depending upon
262 the required dosage of the formed strip. In the majority of the cases, the strips are rolled and
263 stored for a certain time before cutting, which is known as 'rollstock' in an industry.
264 However, a film should not be exposed for too long time since it is prone for being damaged.
265 If possible, it should be cut and packed immediately after the preparation to keep its stability
266 [17]. Several advantages such as better physical properties, easy and low cost processing, and
267 excellent uniformity of thickness are observed with the film obtained by solvent-casting [50].
268 However, this process suffers from some limitation. For instance, a polymeric thin film
269 prepared by solvent casting method was brittle upon storage, as marked by decrease in the
270 percent elongation due to evaporation or loss of the residual solvent in the film over time
271 [51]. Another issue under scrutiny associated with this method is the requirement of using
272 organic solvents. The presence of organic solvent system is a serious problem because it
273 causes a hazard to health and environment. As a result, strict regulations have been adopted
274 by many countries regarding the use of an organic solvent [11].

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

283

284 *6.2. Hot-melt extrusion (HME)*

285

286 HME is a versatile method adopted for the manufacture of granules, tablets, pellets [52],
287 and also thin films [38]. It is a substitute method to solvent casting for the preparation of the
288 film, especially useful when no organic solvent system is required [10]. However, only few

10

289 literature has reported the use of holt-melt extrusion for the preparation of polymeric thin

290 films [11]. HME is a process of shaping a mixture of polymers, drug substance, and other

291 excipients into a film by melting all the components [3]. Eventually, the films are cut into a

292 particular shape and dimensions [6]. In this method, a mixture of pharmaceutical ingredients

293 is molten and then charged through an orifice (the die) to obtain homogeneous matrices [11].

294 Since APIs are subjected to operation at high-temperature with complete absence of solvents,

295 this method is not suitable for thermos-labile APIs [17]. The practical steps of HME are

296 outlined as follows [53]:

297 (i) Feeding of the components to the extruder through a hopper,

298 (ii) Mixing, grinding, and kneading,

299 (iii) Flowing the molten and blended mass to the die, and

300 (iv) Extruding the mass through the die and further downstream processing

301 The equipment for the process of HME is illustrated in **Fig. 3,** which consists of the

302 hopper, extruder, film die, and roller. The extruder contains one or two rotating screws (co-

303 rotating or counter rotating) inside a static cylindrical barrel. The barrel is often manufactured

304 in sections to shorten the residence time of the molten material. The sectioned part of the

305 barrel is either bolted or clamped together. Similarly, the end portion of the barrel is

306 connected to the end-plate die, which is interchangeable depending upon the required shape

307 of the extruded materials [1].

308 With regards to the advantages of HME, it produces a drug in the form of solid dispersion

309 or solution, which could improve solubility of poorly soluble drugs [51]. However, at

310 elevated temperature, there is a high chance of recrystallization of API in the polymer blend

311 as the temperature drop. Using highly viscous molten polymer plasticizer can prevent this

312 problem. Another issue of HME is "Die swell phenomenon" i.e. an increase in the cross-

313 section of the film after ejection from the die depending on the viscoelastic characteristics of

314 polymers. This is due to polymer withstanding high energy kneading and high shear force

315 during extrusion. This problem can be prevented by slowing the speed of screw operation or

316 by gently mixing molten mass for a long time instead of high shear kneading for a short

317 duration [54]. Unlike solvent casting, this method avoids the need of organic solvent; hence,

318 they are proven to be environment friendly [2].

319

320 *6.3. Printing technologies*

321

11

322 Novel methods such as 3D printing could be used for manufacturing polymeric thin films.

323 It could potentially be a platform for producing the dosage form beneficial to the individual

324 patient. This possibly will resolve the issue of the pharmaceutical industry and pharmacies to

325 meet the future demand of customized medicine [55]. The printing technologies are

326 increasingly gaining popularity because of its flexibility and cost-effectiveness. From the

327 viewpoint of pharmaceutical industry, printing technologies are commonly in practice for

328 identifying or labelling of the pharmaceutical dosage forms, particularly to optimize the

329 product to be readily identified and to prevent counterfeit production. However, this approach

330 has recently been adopted for the drug loading of pharmaceutical dosage forms [3]. The

331 examples include the use of off-the-shelf consumer inkjet printers in which drug-loaded inks

332 are deposited to yield accurately dosed units of pharmaceutical ingredients. In addition, a

333 combination of inkjet and flexographic technologies has been practiced as well [55]. The

334 inkjet printing was used for printing of API on different substrate, whereas the flexographic

335 printing was employed to coat the drug loaded-substrate with a polymeric thin film [56].

336 Anhauser et al. made an attempt to load transdermal patches with drug substances *via*

337 screen printing and pad printing; however, pad printing was limited by the low speed of

338 production. In recent years, inkjet printing has made inroads for preparation of film

339 formulation as a safe and accurate method to produce dosage form of potent drug

340 administered at low dose [57]. Preparation of multiple layer can be done by adding a second

341 printing layer on the top of the first with or without an intermediate base film layer. Further,

342 the printed layer would be shielded by a second base film layer. This will result in modified

343 drug release profiles and protect the ink layer from detachment or mechanical stress during

344 processing like cutting or packaging area [55].

345 Regardless of the various types of printing technique used, all of them contribute to

346 producing a film with more homogeneous distribution and accurate dosage of the drug

347 throughout the films. The dose accuracy and uniform distribution of the drug substances in

348 the films are accounted for several reasons, such as coating mass properties, like viscosity or

349 density, which are inherently influenced by the amount and characteristics of the processed

350 drug substances. With regards to the conventional method of film preparation, it may be very

351 challenging to ensure the same dosage accuracy in the individual units [3]. To summarize,

352 printing a drug on dosage form is the latest intervention for film preparation and it has

353 become a powerful tool to manufacture dosage form with excellent uniformity, speed-ability,

354 and stability. Representing printing technologies that have been used for preparation of

355 polymeric thin films are discussed below.

12

356

6.3.1. Inkjet printing

358

359   Inkjet printing is the recently developed technology, which is characterized by its
360   versatility, accuracy, repeatability and relatively inexpensive method that deposits small
361   volumes of solution in films. Inkjet printing is extensively applicable for the preparation of
362   low dose medicines and also offers an opportunity to manufacture personalized medicines
363   [58].

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

377   The uniform distribution and dose accuracy of the drug substance in the film rely upon the
378   density or viscosity of the ink (drug substance solution or suspension), which determine the
379   printability characteristics [3]. Buanz et al. (2011) demonstrated the deposition of low doses
380   of salbutamol sulphate onto commercially available starch-based film using conventional
381   desktop printers [10]. However, inkjet printing is not applicable for high-throughput
382   industrial production, instead using of flexographic printing is regarded more suitable for
383   industrial preparation.

384

6.3.2. Flexographic printing technology (FPT)

386

387   FPT is a process that transfers active pharmaceutical ingredient into thin films gently *via*
388   contact printing [10]. The flexographic printing is a rotary printing process as depicted in **Fig.**
389   **4**, where ink consisting of drug substance solution and suspension is measured by an anilox

13

390 roller then are transferred to a printing cylinder that prints the film after unwinding the
391 daughter roll [3]. It is useful for heat sensitive products like proteins and peptides. As the
392 mixing and drying of film formulation are processed before introducing the drug, the
393 problems such as loss of activity of API can be prevented. The production efficiency is also
394 high considering the production rate of 530 oral films per min, hence this process could be
395 expanded to scale-up production [6]. No effect on the mechanical properties of polymeric
396 thin films upon printing drug solutions was witnessed using flexographic printing [57]. In a
397 study, Janßen et al. (2013) found that it was possible to dispense tadalafil and rasagiline
398 mesylate solution onto hydroxypropyl methylcellulose films using flexographic printing. The
399 introduction of hydroxypropyl cellulose appeared to reduce drug crystallization after printing.
400 However, the main drawbacks of flexography are relatively low resolution, high chances of
401 contamination, and the need to prepare a print roller, which is not suitable for large scale
402 production [10].

403

404 **7. Quality issues of thin films**

405

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

413

414 *7.1. Thickness and weight variation*

415

416 The measurement of thickness is necessary as it directly correlates with the amount of drug
417 in the film. In addition, an appropriate thickness is required for the comfortable
418 administration of films. For instance, the ideal thickness of buccal films should be in the
419 range of 50 to 1000 μm [12]. Generally, the thickness of the formed thin films is measured
420 using Vernier caliper, electronic digital micrometer, screw gauge, or scanning electron
421 microscopy (SEM) images [60, 61]. The amount of plasticizer in the formulation is known to
422 increase the film thickness slightly [62]. By inserting m (Batch) – the mass of the whole

14

423 batch, m (API/film) – the drug amount per film, ρ (Batch) – the density of the formulation, m

424 (API) – the total drug amount in the batch and A (Film) – the area of one film in **Eq. (1),** it is

425 possible to calculate the casting thickness (h). A correction factor f is added due to the shift of

426 actual value of film thickness compared to the set values. A shift behavior is defined

427 beforehand over different coating thicknesses [63].

428

$$H\ (\mu m)\ =\ \frac{m\ (Batch)\ \times\ m\ (API/film)\ \times\ 10{,}000}{\rho\ (Batch)\ \times\ m\ (API)\ \times\ A\ (film)} \tag{1}$$

429

430

431 where, API is active pharmaceutical ingredient, m is mass, ρ is density, and A is area

432 expressed in g, g/cm^3, and cm^2 respectively.

433

434 The weight variation is generally carried out to ensure that each film contains the

435 consistent amount of a drug without significant deviation. It is calculated by weighing the

436 individual film and the average weights of specified films respectively. The average weight

437 of film is subtracted from the individual weight of patches. The mean ± SD values are

438 calculated for all the formulations. A large variation in weight signifies the inefficiency of the

439 method applied and high chances are there for non-uniformity in drug content [12].

440

441 *7.2. Mechanical and physical properties*

442

443 Polymeric films should possess enough tension so that it can be ejected easily from the

444 pouch, rolled up after casting, and peeled from the release liner, but should not be too flexible

445 because greater elongation during cutting and packaging might cause variation in film

446 amount resulting in non-uniformity of API amount per film [49, 64]. Mechanical properties

447 of films can be defined in terms of Young's modulus, percent elongations, tensile strength

448 and tear resistance [64, 65]. It has been known that soft and weak polymers exhibit low

449 tensile strength, low elongation at break and low Young's modulus, whereas, the hard and

450 tough polymer have a high tensile strength, high elongation at break and high Young's

451 modulus [11]. Additionally, the mechanical properties of films are affected by the method of

452 manufacturing and the formulation. In general, some examples of behavior attained from

453 stress strain curves are showed in **Fig. 5** [6]. The concentration and types of the polymers are

15

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 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 over-hydrating 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, 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

16

487   outcome [74]. The tensile strength is calculated by using several parameters such as folding

488   endurance, percent elongation, elongation at break and Young's modulus.

489

490   *7.2.1. Folding endurance*

491

492   The flexibility of thin film is important when considering that the films can be

493   administered without breakage. The flexibility of the polymeric thin films can be measured

494   with respect to its folding endurance. The folding endurance is determined by folding the film

495   repeatedly at 180° angle of the plane at the same place until it breaks or folded to 300 times

496   without breaking [75].

497

498   *7.2.2. Percent elongation and elongation at break*

499

500   Elongation, a kind of deformation, is a simple change in shape that any objects encounter

501   under any applied stress. In other words, when the sample is subjected to tensile stress,

502   deformation of the sample takes place resulting in stretching or elongation of sample [17].

503   Measurement of elongation is generally done to predict the ductility of polymers [65]. Elastic

504   elongation or ultimate elongation of a sample can be measured by using a texture analyzer.

505   Elastic elongation is phenomenon shown by all kinds of elastomers. The percent elongation

506   indicates the stretch ability of material without being broken; whereas, elongation at break

507   means the point until which the film can be stretched when it is torn (or broken) by the

508   applied probe (**Fig**. 7). With the exertion of stress to a sample, strain generates, and the

509   sample elongations will become more predominant as the amount of stress applied increases.

510   However, after reaching to a certain point the sample breaks, this point of breakage is

511   referred as percent elongation break [76]. The formula for percent elongation is given in **Eq.**

512   (**2**) as under:

513

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

514

515

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

517

518

17

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

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, 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 which 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 following formula:

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

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.

18

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 the 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 Fisher titration or by weighing method. In weighing method, pre-weighed 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. The **Eq. (5)** is used for calculating the amount of moisture content in the film that is expressed as % moisture is given below [12]:

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

7.4. Swelling

Swelling properties of films 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

19

579 penetration is also difficult to occur. When the number of hydrogen bonds as well as the
580 strength between the polymers increases, the diffusion of water particles into the hydrated
581 matrix occurs at a slow rate [83]. This was demonstrated by Panomsuk et al., where he
582 reported that introduction of mannitol to methylcellulose matrix decreases the swelling index
583 of the membrane. This may be due to the formation of hydrogen bonding between drugs and
584 the polymeric matrix [84].

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

595

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

596
597

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

602

$$\text{ASR} = \frac{A_t}{A_0} \qquad (7)$$

603
604 where, A_t is area of the film at time t, and A_0 is area of the film at time zero.

605
606 *7.5. Drug release profiles*

607

20

608   To a great extent, the release kinetics of drugs from the polymer matrix is primarily
609   dependent on the physicochemical properties of the materials used as well as the morphology
610   of the system [36]. Variation in pH or temperature may cause increase or decrease in the
611   erosion or dissolution rates of polymers [88]. Upon contact with biological fluids, the
612   polymeric film starts to swell following polymer chain relaxes resulting in drug diffusion.
613   The release of drug holds a direct relationship with polymer structure; for example, linear
614   amorphous polymers dissolve much faster than cross-linked or partially crystalline polymers
615   [89]. According to several studies, the release of the drug is markedly influenced by erosion
616   of the film. The degradation rate of the film is also dependent on the types of plasticizer [11].
617   For the drug to penetrate the biological membrane, the drug should be released from the
618   delivery systems at an optimum rate. Assessing the drug release from the film is essential as
619   it is the rate-determining step in the process of absorption. The dissolution of drugs and/or
620   films is assessed with the apparatus that are approved for other solid dosage forms [90].

621   In the literature, many authors have done some improvisation on the dissolution apparatus,
622   while others have employed Franz diffusion cells (FDC) for testing the drug release from the
623   polymeric films [12]. A major barrier with respect to film in dissolution testing is the placing
624   of the samples. Several methods have been practiced, where the film are attached on the inner
625   side of the glass vessels or the stirring element using an adhesive tape [91]. Okamoto et al.
626   (2001) conducted a dissolution study of lidocaine film for buccal administration using a JP
627   XIII dissolution apparatus at $37\pm 0.1°C$. A film was cut into a circle having an area of 1 cm^2
628   and adhered to a 3 cm diameter weight using double adhesive tape. Then after, the film with
629   weight was placed in a glass vessel filled with 500 ml of artificial saliva so that film dosage
630   form faces upwards as shown in **Fig. 8** [92].

631

632   *7.6. Surface morphology*

633

634   The morphology of the film should appear homogeneous and continuous to ensure the
635   uniform distribution of drug throughout the polymeric mixture. Self-aggregation might take
636   place during drying because of the intermolecular and convective forces leading to wrinkled
637   surface in films. Additionally, interaction between drug and polymers, and the crystalline
638   nature of the drug may result in the formation of rough surface in the films [93]. Hence,
639   assessing the surface morphology and texture is crucial to assure uniform distribution of
640   drugs without any interaction with the polymers in the film formulation. Various surface
641   characteristics such as surface texture (smooth or rough), thickness, and drug distribution

21

642 (aggregated or scattered) of the film can be observed using light microscopy, scanning

643 electron microscopy (SEM), transmission electron microscopy (TEM) and related imaging

644 techniques [83]. Amongst all, the scientists have more clung to SEM as a reliable method for

645 examining the surface morphology of the films. The operation is carried out by mounting the

646 films on stubs, sputter coated with gold in an inert environment and subsequently, the

647 photographs are taken at a suitable magnification. This approach can be utilized for close

648 observation of size, shape and the number of pores on the surface of polymeric films. Most

649 recently, there are number of studies on the use of SEM in evaluating the role of chemical

650 composition of the film on the crystallinity, morphology and texture [12].

651

652

653 **8. Packaging of thin films**

654

655   Packaging is crucial to provide mechanical protection as well as to keep the stability of

656 thin film formulations. It acts as a barrier to the moisture, light, and oxygen. A number of

657 choices are available for packaging the polymeric thin films, but not all are effective to

658 preserve the integrity and physical properties of the product. Aluminum foils are most

659 commonly used and considered ideal for film packaging as it prevents the film from moisture

660 and light degradation. Similarly, lidding foil has been employed if tamper proof packaging is

661 needed. Films are subjected to multi-track sealing to achieve an accurate airtight seal between

662 the upper and lower pack foils [17]. The most commonly available sizes of films are 3 x 2

663 cm^2 and 2 x 2 cm^2. The packaged films are checked thoroughly before being packed into a

664 secondary packaging container [22]. The packing of manufactured film in foil, paper or

665 plastic pouches is cost-effective, easy to handle, and allows easy formation of the flexible

666 pouch by either vertical or horizontal forming method during product filling [4].

667   Nowadays, the strips are available in both single dose sachets and multiple-unit blisters. A

668 single dose sachet with a name Pocketpaks™ for cool mint Listerine was introduced by

669 Pfizer consumer healthcare. Similarly, a tear notch/slit/cut-off is manufactured to ensure

670 convenience for the consumer to peel-off the pack. This technique is automated and

671 computer-driven process [17]. APR-Labtec launched a patented packaging system with the

672 name Rapid card for the Rapid® films. The rapid card has same size as a credit card and

673 contains three films on each side, which can be removed individually [22].

674

22

9. Routes for the administration of thin films

9.1. Oral route

Developing polymeric films have made 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 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].

Squier and co-workers reported that 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 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 time 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, 97]. 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.

23

709   Films containing the polymeric blend would be an ideal platform for the delivery of drugs

710   in the oral cavity because of its comfort and flexibility [98]. Over the last decade, there has

711   been an enormous rise in the development of buccal films as an alternative drug delivery for

712   various classes such as anti-inflammatory, analgesics, anesthetic drugs and proteins and

713   peptides. Of recent, mucoadhesive films have been used as a delivery platform for

714   transmucosal buccal delivery of Biopharmaceutics Classification System (BCS) Class II

715   drugs particularly targeting the opioid analgesics like fentanyl citrate, which is available with

716   a trademark name such as Onsolis®/Breakyl® for treating immense pain [26]. Similarly, the

717   mucoadhesive film remains attached to the buccal area without showing any erratic

718   absorption profile resulting in less inter and intra-individual variability [72]. Oral thin films

719   (OTFs) are comparable to the disintegrating system, which is soaked in saliva and stick to the

720   site of application. The rate of disintegration is rapid allowing the drug to release and

721   followed by the oromucosal absorption. Many drugs that undergo degradation in the GI tract

722   are being administered employing this route [99].

723   In context to the commercially marketed product of the oral thin film, the nutraceuticals

724   and over-the-counter drugs were among the first to be introduced in the market, and included

725   the incorporated active such as vitamins, herbal and non-herbal extracts. In 2001, Pfizer

726   introduced a thin film product of Listerine pocketpaks® developed as mouth freshener. The

727   company Bio-film has been putting an endeavor to develop oral thin films. Not only the

728   pharmaceuticals but they are also using nutraceuticals such as vitamins, aphrodisiac, energy

729   boosters, and appetite suppressor that targets a specific population of the certain age group.

730   The energy booster consists of various compounds such as caffeine, guarana, and green tea

731   extract to maintain the energy levels [17]. A number of companies have been attempting to

732   develop a drug delivery platform based on polymeric films. Most of them have already

733   succeeded in obtaining a film with rapid release along with better therapeutic outcomes [2].

734   The companies with their technology platform based on polymeric film are listed in the

735   **Table 2.**

736

737   *9.2. Ocular route*

738

739   More than 90% of the marketed ocular formulation are in the form of solutions or

740   suspension; however, this conventional dosage form lacks to achieve promising therapeutic

741   success [100]. The frequent instillation of eye drops is needed to elicit a therapeutic response.

742   This usually leads to patient non-compliance and pulsed administration. Furthermore, the

24

743 topically applied drugs to the eye generally enter the systemic circulation *via* the nasolacrimal

744 duct system that possibly cause side effects and systemic toxicity as well [101]. With the aim

745 of enhancing the ocular bioavailability and overcoming the ocular drug delivery barriers, the

746 development of ophthalmic film becomes popular these days [84]. The ophthalmic films

747 result in the reduction of dose frequency, less systemic side effects and better therapeutic

748 outcomes. Therefore, ophthalmic films could open the exciting opportunities as a delivery

749 platform of therapeutics to replace the traditional dosage forms for achieving high therapeutic

750 success and patient adherence. So far, the list of drugs formulated in ophthalmic films is

751 presented below in **Table. 3.**

752   The flow of tear across the outer surface of the cornea is continuous, which impedes the

753 drug diffusion leading in low bioavailability (1-7%) of drugs [109]. Generally, the drug with

754 higher lipophilicity encounters many problems as it cannot be dissolved in the aqueous

755 medium of the eye. Since the drug causes discomfort in the eye, it induces blinking and

756 therefore, causing washing out of the significant amount of drug. Therefore, the success of

757 the effective development of films to be delivered to the eye relies on the comprehensive

758 knowledge of the drug, the constraints to ocular drug delivery, and the excipients used.

759 Hence, all these factors should be considered during the formulation of ocular films.

760

761   *9.3. Transdermal route*

762

763   Drug-loaded transdermal films are the alternative to replace the existing transdermal

764 dosage form. Numerous sustained or controlled delivery systems have been devised, where a

765 drug is either dissolved or dispersed in the films [71]. The film-forming system has been

766 practiced for the transdermal delivery of steroidal hormones, analgesics, local anesthesia and

767 anti-emetic for systemic effects [110, 111, 112].

768   Only a small number of drugs are being designed for the transdermal delivery of films as

769 several factors affect the bioavailability of drug such as molecular size, polarity, pH of the

770 drug, state of the skin hydration, subcutaneous reservoir of drug and drug metabolism by skin

771 flora [113]. Similarly, the hydration of skin is crucial for increasing drug absorption, which is

772 possible by using humectant in the film formulation. The physiological factors such as

773 regional skin site, nature of stratum corneum, the thickness of skin, and density of

774 appendages also influence the overall outcome of the therapeutic effects of the drug [114].

775   The thin film may possess better therapeutic efficacy and patient acceptance compared to

776 the common transdermal dosage forms such as patches or gels [115]. Due to occlusive

25

777 properties of transdermal patches, it prevents the permeation of water vapour from the skin

778 surface and causes severe pain at the time of peeling. However, polymeric thin films could be

779 a highly promising alternative for transdermal drug delivery because of the ease of

780 application, flexibility and better cosmetic appearance [29].

781

782 **10. Future scope of development and conclusion**

783

784 The formulation of a drug into various films has been popular in recent years. Several

785 undesirable drawbacks associated with conventional dosage forms such as inconvenience of

786 administration, lower bioavailability and patient non-compliance have pushed to the

787 development of novel polymeric thin films as a drug delivery platform. This drug delivery

788 platform is being under surveillance from both start-up and established pharmaceutical

789 companies. The companies strive to design a wide range of thin films for oral, buccal,

790 sublingual, ocular and transdermal routes. Therefore, as an alternative to conventional dosage

791 forms polymeric thin films are expected to stand out as a dosage form to overcome the

792 limitations posed by existing dosage forms. The film dosage form encounters several

793 challenges during the phases of formulation development and manufacture. Such issues

794 should be addressed to optimize the overall formulation even after transferring to large scale

795 manufacturing. The future looks very promising for the film technology in the time to come

796 as new technologies are rapidly introduced to prepare thin films.

797

803

804 **Conflict of Interest**

805 The authors declare no conflict of interest.

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Figure legends

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 Amin et al., 2015 [22])

Fig. 3. Holt-melt extrusion system for the preparation of films (reproduced from Amin et al., 2015 [22])

Fig. 4. Schematic overview of flexography technology for the preparation of films (reproduced from Janßen et al., 2013 [57])

Fig. 5. Examples of stress-strain curves obtained from polymeric thin films (reproduced from Morales & McConville, 2011 [11])

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 Preis et al., 2014 [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]

Fig. 8. Schematic illustration of the apparatus used for dissolution studies of films. The film dosage form (1 cm^2) was attached to a 3 cm diameter weight using double adhesive tape (reproduced from Okamoto et al., 2001 [92]).
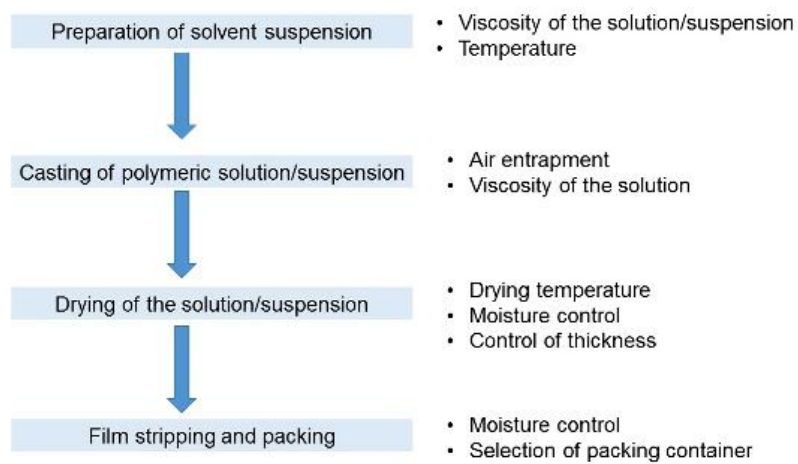
Fig. 9. Demonstration of common site for application of film in buccal and sublingual mucosa (reproduced from Lam et al., 2014 [97])

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1098   **Fig. 1**

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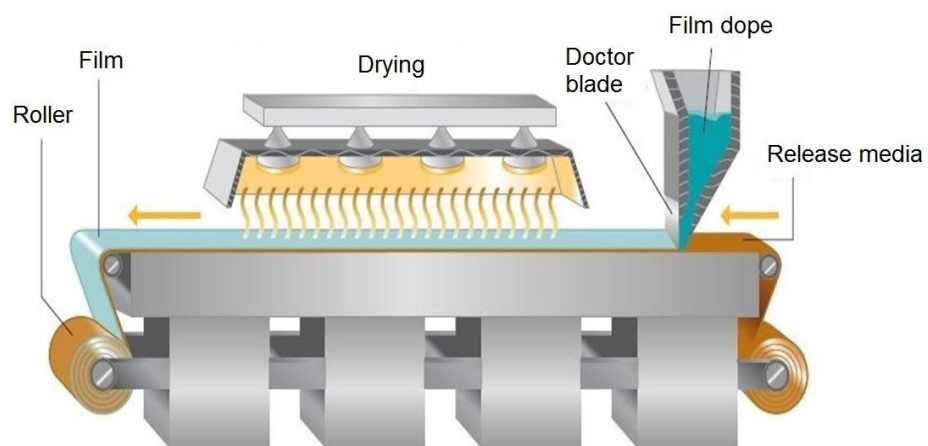- Preparation of solvent suspension
  - Viscosity of the solution/suspension
  - Temperature

- Casting of polymeric solution/suspension
  - Air entrapment
  - Viscosity of the solution

- Drying of the solution/suspension
  - Drying temperature
  - Moisture control
  - Control of thickness

- Film stripping and packing
  - Moisture control
  - Selection of packing container

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1102 **Fig. 2**

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1107   **Fig. 3**

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Hopper

Film die

Extruder screw

Film

Motor

Roller

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1111   **Fig. 4**

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Drug containing ink   Printing cylinder   Drug-free films

Anilox roller   Impression   Fan   In process   Drug-printed films
                     cylinder   control

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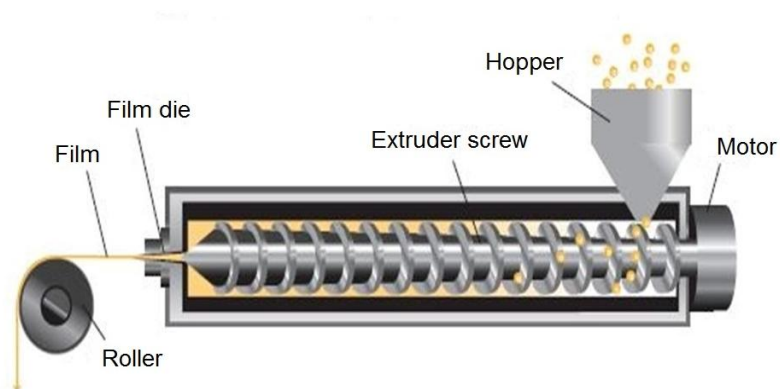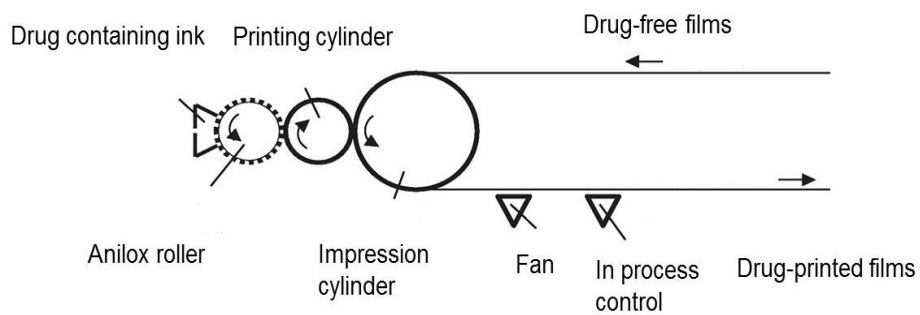
1116 **Fig. 5**

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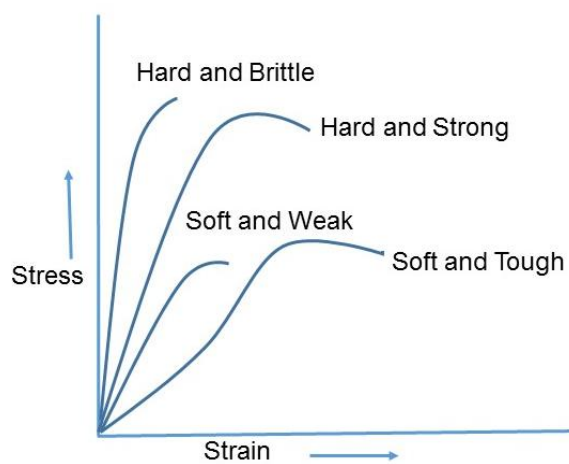
1121   **Fig. 6**

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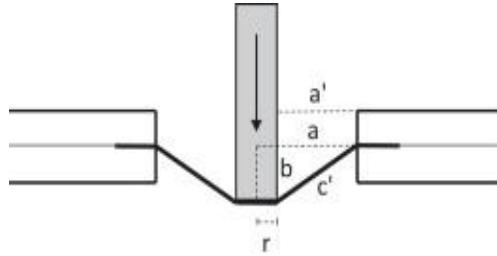
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1125 **Fig. 7**

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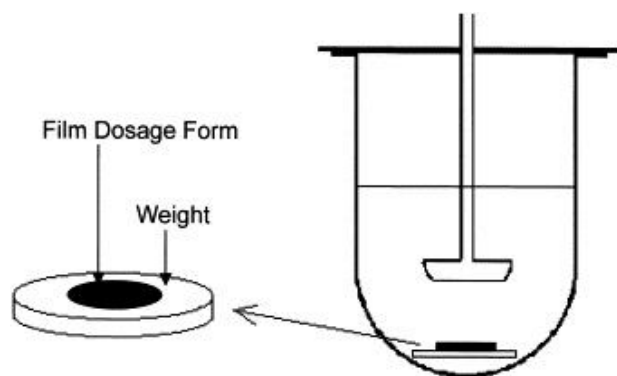
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1130   **Fig. 8**

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Film Dosage Form

Weight

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1135   **Fig. 9**

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Site of drug administration at the buccal mucosa

Site of drug administration at the sublingual mucosa

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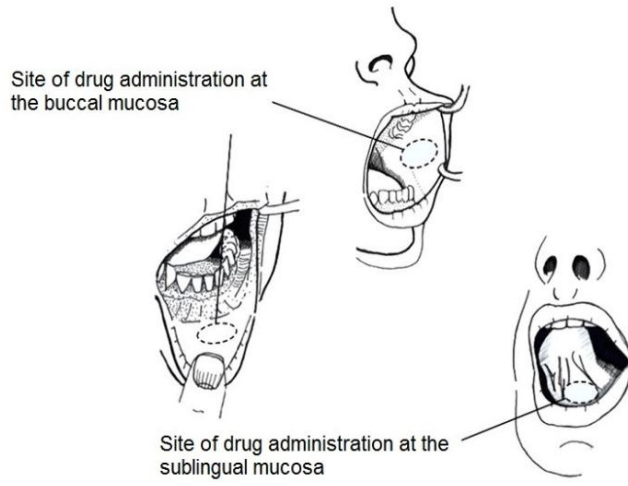
Tables

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 improve film forming ability • Blended with ethyl cellulose and HPC produce 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	• Very flexible films • Mainly used in ophthalmic polymeric preparations at	[3]

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	• Water soluble synthetic polymer • Non-ionic polymer • Moderate mucoadhesive properties	concentration 3-5% • Higher elongation at break values	
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 enhance 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]
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]

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| 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 in the 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] |

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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)	
BioAlliance Pharma	Setofilm®	Ondansetron ODF	[21]
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	
MonoSol Rx	Suboxone®	Buprenorphine and naloxone (sublingual film)	
C.B. Fleet	Pedia-Lax™ Quick Dissolve Strip	Sennosides ODF	[55]
Novartis Consumer Healthcare	Gas-X Thin Strips	Simethicone (sublingual film)	
Pfizer	Sudafed PE quick dissolve strips	Phenylephrine ODF	

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1142 **Table 3.** List of drugs used in ocular films

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Active agent in ocular film	References
Acetazolamide	[102]
Timolol maleate	[103]
Ofloxacin	[104]
Dorzolamide hydrochloride	[105]
Levofloxacin	[78, 106]
Naphazoline HCl	[107]
Natamycin	[108]

Comment [A1]: Author: There are two table 3 captions were provided in the manuscript and this has been retained. Please check and confirm it is correct.

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