Available online at www.jobpcr.com

ISSN-2394:3076
CODEN(USA) : JBPCBK
Journal of Biological Pharmaceutical And Chemical Research , 2022, 9(2): 75-86

(http://www.jobpcr.com/arhcive.php)

Current review on thin films: A potential carrier of medicaments

Yamini Srinivas Gali [1], Mohan Varma Manthina [2], Radha Madhavi Baluguri [1], Vasu Peddinti[1], Abbas Ali [2], Krishna Prasad Davarasingi [1], Ashok Thulluru [1*]

[1]Dept. of Pharmaceutical Quality Assurance, Shri Vishnu College of Pharmacy (Autonomous), Vishnupur, Bhimavaram-534 202, West Godavari Dist., Andhra Pradesh, India.

[2]Dept. of Pharmaceutics, Shri Vishnu College of Pharmacy (Autonomous), Vishnupur, Bhimavaram-534 202, West Godavari Dist., Andhra Pradesh, India.

Corresponding Author: ashokthulluru@gmail.com

ABSTRACT

Thin films are flexible layer of polymer that contains or does not contain a plasticizer and is used as a potential carrier of drugs from longer periods. Oral thin film, Oro-dispersible film, oral soluble film, wafer, oral strip, buccal film, mucoadhesive film, ocular film, and transmucosal film are some of the names given to thin films. In this current review various formulation additives, advantages, disadvantages, manufacturing technologies, evaluation studies, route of administration and future perspectives of thin films are discussed.

Key words: Thin films, Oral thin film, mucoadhesive film, evaluation studies, manufacturing technologies and future perspectives.

INTRODUCTION

Thin film is defined as a slender, elastic layer of polymer which consists or does not consist a plasticizer [1]. Due to its elasticity, the patient may consider them as less conspicuous and more tolerable [2]. A thin film is made up of matrices of different polymers that meet a number of criteria for being an effective drug delivery route [3]. Basically, thin films are great options to target the sensitive sites that tablets or liquid formulations may not be able to do [4]. They have significantly showed its ability to enhance medication's duration of action, decrease the frequency of dose, and improve the effectiveness. Thin films may be effective to decrease the excessive metabolism produced by proteolytic enzymes and eliminates pharmacological adverse effects [5, 6].

Types of thin films: thin film does not come under a new formulation as it was first launched in late 1970 to alleviate the swallowing problems associated with capsules and tablets [3]. Thin films include Oral thin film (OTF), Oro-dispersible film (ODF), oral soluble film, oral strip, buccal film,

wafer, mucoadhesive film, ocular film, and transmucosal film. Numerous films are designed to dissolve rapidly in the mouth such that a medicine can be absorbed into the gastrointestinal system (ODFs). Several patients are interested to take the medications that deliver the drug at the site of administration (e.g., ophthalmic, sublingual and buccal thin films). Drugs possessing greater mucosal permeability have found to be acceptable for buccal and sublingual film administration [7]. The thin films which are intended to be delivered to the eye are commonly used in the treatment of diseases of anterior chamber such as pink eye, glaucoma and keratoconjunctivitis sicca [5]. As per European Medicines Agency (EMA), a film which rapidly dissolves in the oral cavity is known as Oro dispersible film, or a soluble film as per Food and Drug Administration (FDA). Rapid dissolving oral films are usually ultra-thin in nature (50-150 m) similar to a postage stamp in terms of size, and disintegrates in the oral cavity within a minute after coming into contact with saliva, thus results in rapid absorption and bioavailability of the drug [8, 9]. Drugs kept in buccal cavity in the form of adhesive films can be absorbed through the buccal mucosa directly, which transports the drug into the systemic circulation [10]. Wafer is also referred to as a paper-thin polymeric film used as a carrier of medicaments. It is given and taken orally, does not require the swallowing of water for the drug's absorption [11]. ODFs should not be confused with buccal films meant to stay on the cheek mucosa for prolonged periods of time [12]. As a result, different sorts of films must be distinguished precisely to avoid misinterpretations.

MATERIAL AND METHODS

Formulation:

- **Active pharmaceutical ingredient (API):** ODFs are thin, fast-dissolving films with an area of 5 to 20 cm^2 in which the medication is embedded as a matrix utilising a hydrophilic polymer. Plasticizers, colourants, sweeteners, flavour masking agents and other excipients can be added up to 15 mg of active medicinal component. Plasticizer improves the workability, spread ability and flexibility of films, reduces the polymer's glass transition temperature. The general composition in ODFs is represented in (Table1). APIs (Antihistamines, anti-diarrheal, anti-depressants, vasodilators, anti-asthmatics, anti-emetic drugs) and so on can also be added into ODFs. Salbutamol sulphate, rizatriptan benzoate, verapamil, ondansetron, dexamethasone, rofecoxib, cetirizine, pilocarpine, tianeptine sodium, indomethacin, and other medicines are commonly found in ODFs.

Table.1. General composition of ODFs

Components	Concentration (%)
API	1-25
Hydrophilic polymer	40-50
Plasticizer	0-20
Colour, filler, flavour	0-40

- **Hydrophilic polymers**: Effectiveness of an ODF mainly depends on the choice and concentration of the polymers owing to its film strength. The polymer thus selected should possess defined qualities to be used as film former in the development of thin strips. Natural and Artificial

polymers have been widely used in the development of ODF's formulations in recent years as mentioned in (Table 3). Non -irritantancy, non-hindrance with the disintegration time, affordability, good mechanical properties and non-toxicity are the Ideal properties of hydrophilic polymers

Table. 2. Most commonly used hydrophilic polymers in ODFs

Type of polymer	Examples
Natural	Starch, Polymerized resin, Pullulan, Sodium alginate, Pectin, Gelatin, Maltodextrins
Synthetic	Polyvinyl alcohol, Hydroxy propyl methyl cellulose, Sodium carboxy methyl cellulose, Polyvinyl pyrrolidone, Hydroxy propyl cellulose

- **Plasticizers:** In general, adding plasticizer to formulations improves mechanical qualities like as tensile strength and % elongation. Plasticizer concentrations typically vary from 0% - 20% on overall bases. Some of the examples include PEG, glycerol, diethyl phthalate, triethyl citrate, tributyl citrate, and other plasticizers.

- **Surfactants:** Surfactants are important as they act as a dispersing, wetting, and solubilizing agents; allows a film to breakdown in seconds and release the integrated medicine rapidly. Benzalkonium chloride, tweens, and sodium lauryl sulphate are commonly used surfactants. Because of its numerous benefits, Poloxamer 407 is frequently utilised.

- **Flavour:** To disguise the bitter or unpleasant taste of the integrated medication, flavours are required. The strength and character of the flavour determine the amount of flavour. Any flavour such as sweet, sour or mint which are approved by US-FDA can be used. One study found that a mixture of mint, liquorice, and sucralose effectively masks the bitter taste of medicaments.

- **Sweeteners**: Sweetening agents are made to dissolve or disintegrate in the mouth. Sweeteners which are synthetic and natural are utilised in the preparation of ODFs as mentioned in (Table 3). Sugar is 2000–8000 times sweeter than neotame and alitame. In comparison to sorbitol and mannitol, fructose has a higher sweetening capacity. When several marketed ODFs were tested for taste, aftertaste, and tongue feel, sucralose showed 600–1000 times sweetness than sucrose. Saccharin sodium and Aspartame are believed to be 200–500 times sweeter in comparison to sucrose. Sweeteners and flavours are also said to have a modest impact on film elasticity.

Table. 3. Examples of mostly used sweeteners in ODFs

Sweetening agent	Example
Natural	Glucose, Fructose, Dextrose, Sucrose, Isomaltose
Artificial	Acesulfame-K, Sucralose, Neotame

- **Saliva stimulants**: Saliva stimulants are often acidic, aids the disintegration of ODFs by boosting saliva production in the buccal cavity. Some of the most often utilised saliva stimulants include citric acid, malic acid, tartaric acid, ascorbic acid, and lactic acid.

➢ **Colorants:** Pigments have been utilised as colouring agents in ODFs. Titanium dioxide is highly recommended to be used as colourant. A comprehensive spectrum of colours, such as FD&C approved natural, and bespoke pantone-matched colours, are available in addition to titanium dioxide.

Advantages of thin films:

➢ **Benefits over conventional dosage forms:** Thin film degrades more quickly compared to remaining dose types [13]. In comparison to commercialised oral disintegrating tablets (ODTs), which require specific packaging, thin films are less brittle and easier to transport. Similarly, a unit dose of strip can be transported without the need for a backup container [14, 15]. The inadequate stability of liquid dosage forms, particularly water-soluble formulations, must be addressed. In contrary to the thin films, there is a requirement to take precautions during exact determination of the amount, and while shaking the bottle every time prior to the administration, as it may lead to poor patient compliance. Traditional ophthalmic drug delivery systems, like eye drops or solutions are widely used, but they have drawbacks in terms of drug's bioavailability and onset of action at the ocular site [16-18].

➢ **Clinical advantages:** Thin film is preferred by patients because of its appealing shape and convenience of administration. ODFs is also beneficial for paediatric, geriatric, and psychiatric patients because it is simple to use, does not cause choking or suffocating, ensures patient safety. When an immediate onset of action is necessary, such as in the cases of motion sickness, acute episodes of allergy response or coughing, bronchitis, or asthma, OTFs are more beneficial.

Disadvantages of thin films: Thin films use is sometimes restricted, owing to a less drug loading capacity for a less strong agent administered at a high dose [19]. Hygroscopicity of thin films are common in nature. As a result, more care should be made to ensure their long-term preservation [20]. Combining more than one medicine at the same time is a difficult challenge in oral film formulation because the coadministration of a drug in oral films slows down both the dissolving rate and the disintegration time [21]. The inability to acquire high levels of accuracy in terms of the quantity of medicine in each individual unit dose of the film might result in therapeutic inefficacy, non-reproducible effects, and hazardous effects on the patient [22]. The issue of requiring too much time for drying while preparing oral film formulation is a concern. At room temperature, complete drying takes around one day, which significantly slows down the rate of film production. As hot air oven cannot be used for the drugs which are susceptible to heat, consideration about the drying of such drugs should be explored [23].

Technologies to manufacture the thin films: Solvent casting [24, 25] and hot melt extrusion techniques are most widely used processes to produce thin films. Inkjet printing which is an innovative approach has developed in the recent years. The following are detailed descriptions of various polymeric thin film fabrication methods:

➢ **Solvent casting:** Solvent casting is a viable, desirable, and unquestionably extensively utilised form of film making, owing to its easy manufacturing process and less processing costs. The manufacturing technique for thin films using the solvent casting method is depicted in (Fig. 1). The rheological parameters of polymeric mixtures should be considered because they influence the drying rate and thickness of the film [26]. To illustrate with an example, a solvent cast polymeric film undergoes evaporation or gradual loss of residual solvent which will be indicated by reduced percent elongation [9]. The existence of an organic solvent system is a significant issue since it poses both health and environmental risks. Stringent laws have been enacted by several countries

about the usage of organic solvents. Machine used for large-scale film production using the solvent casting technique is depicted in (Fig. 2).

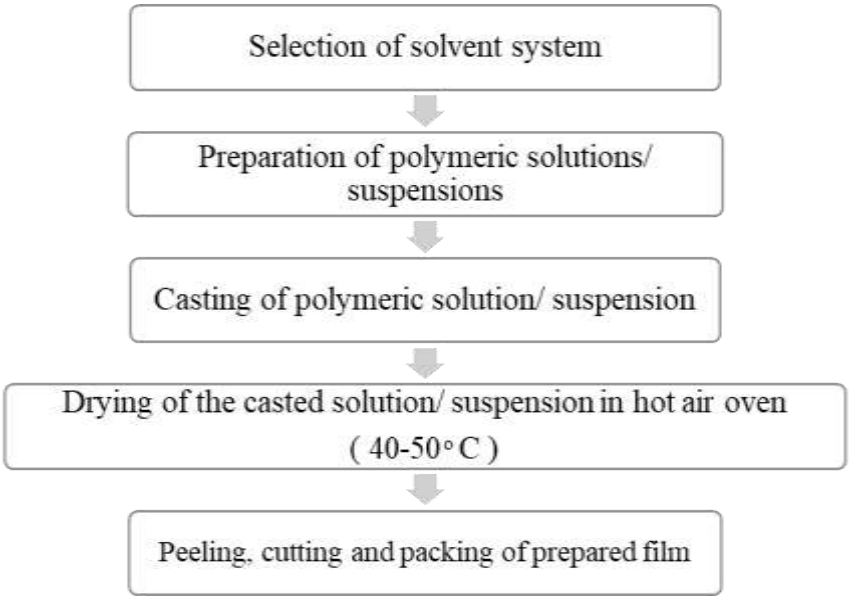

Fig. 1. Solvent casting method to prepare a film using quality control parameters

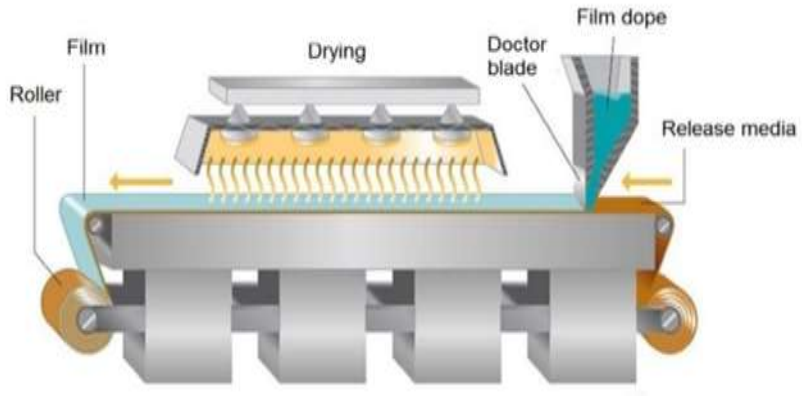

Fig.2. Solvent-casting machine for the commercial manufacturing of thin films

➢ **Hot-melt extrusion (HME):** HME is a flexible process to produce granules, tablets, and pellets [27], thin films. In spite of solvent casting film preparation method can be employed. It is an alternative method of film preparation to solvent casting that can be utilized when organic solvent is not required. HME is a method to melt all of the components of polymeric mixtures, drug materials, and remaining excipients into a film. The films are finally trimmed into a specific shape and size unlike solvent casting, does not require the use of an organic solvent, making it environmentally benign. Hot-melt extruder for the commercial manufacturing of films is shown in (Fig.3)

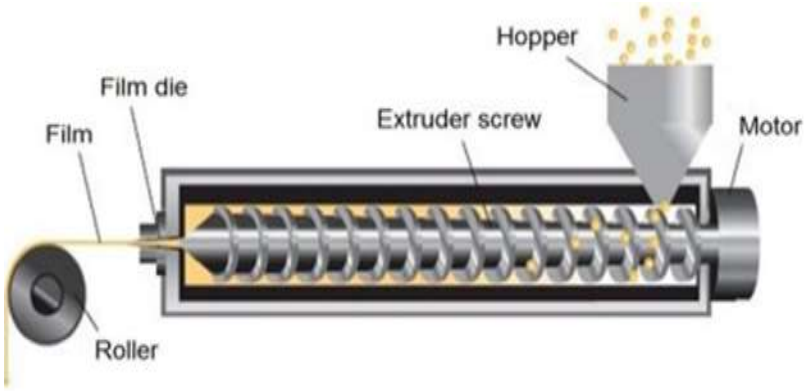

Fig.3. Hot-melt extruder to manufacture commercially the thin films

Printing technologies: Polymeric thin films can be prepared by using newer methods like 3D printing. It could serve as a framework for developing the most effective dose form for a certain patient. Printing technologies are widely employed in the pharmaceutical industry to identify or label pharmaceutical dosage forms, specifically to make the product more easily traceable and avoid counterfeiting. Nevertheless, this technique has been recently used for loading of medicines into pharmaceutical dosage forms [3].

- **Inkjet printing:** Inkjet printing is a relatively new technique that deposits small amount of volumes of solution in films and is characterised by its versatility, accuracy, cost-effectiveness and repeatability. Inkjet printing is widely used in the fabrication of low-dose medicines, and it also allows for the production of individualised medicines. Continuous inkjet printing (CIP) and drop on demand (DOD) printing are the two most common types of inkjet technology. In the instance of CIP, a liquid is consistently ejected out a nozzle (orifice), where it breaks into a stream of drops due to surface tension.
- **Flexographic printing technology (FPT):** FPT is a contact printing technology which softly delivers active pharmaceutical ingredients into thin films. Flexographic printing, as shown in (Fig. 4), is a rotary printing technique in which drug ingredient solution and suspension containing ink is determined by an anilox roller and then sent to a printing cylinder, which prints the film after relaxing the daughter roll.

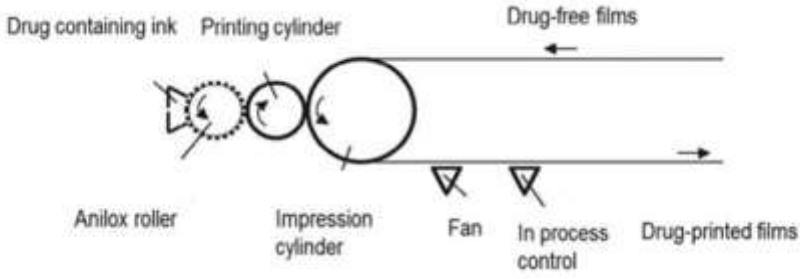

Fig.4. Schematic representation of flexographic printing for the manufacturing of thin films

Characterization of thin films: Is obtained through following tests [9]:

Organoleptic evaluation: For this, specially designed human taste panels are employed. Human volunteers are used in this in vivo taste test. Taste sensors are used for screening in the *in-vitro*

evaluation of taste in the ODFs. For high-throughput taste sensing of dosage forms, in *vitro* assessment methodologies and technologies are adequate and sufficient. Taste masking capability and palatable level of taste masking agents are reviewed using both *in vivo* and *in vitro* methods.

Mechanical properties:

- **Thickness test:** A calibrated "Digital micrometre" is used to estimate the thickness of a film, and a mean average is calculated. In most cases,3 readings from each batch are taken, an average is produced [28].

- **Dryness /tack test***:* This type of test is used to determine a film's capacity to stick to a piece of paper pushed among the strips. The firmness with which a film sticks to the piece of paper or anything supportive crushed between the films is considered as tack. These kinds of tests are mostly used to examine the dryness of films in the paint business, although they can also be used to check orally rapid dissolving films.

- **Tensile strength**: The greatest tension where the film breaks is defined as tensile strength. The objective to conduct the tensile strength test is such that the tensile strength of oral thin films can be estimated.

  - **Percent elongation***:* When a film is stressed, the specimen stretches, is termed as strain. The term "strain" refers to a change in film length divided by the film's original/initial length [29].

  - **Tear resistance:** The complicated function of a film's final resistance to rupture is its tear resistance. The tear resistance value is the maximum force required to rip the film. The plastic industry is usually blamed for this test.

  - **Folding endurance***:* It is an alternative method for the estimation of mechanical properties of the film. It can be calculated by folding a film at the same location over and over until it breaks. Folding the film repeatedly at the same location beyond its capacity to break the film is called as folding endurance value.

Transparency: The transparency of a strip can be found out by UV spectrophotometer. The visual look of the formulation is tested in this test.

Content uniformity: The contents present in a film are determined using a standard assay method described in several pharmacopoeias for each unique drug. Analytical procedures are used to perform this test on 20 samples. According to the Japanese pharmacopoeia, the test's acceptance value is < 15%. According to USP 27, the limits for the content uniformity varies within the range of 85 to 115 %, with ≤ 6% standard deviation. For determining drug amounts in individual films, content uniformity is calculated [28, 29].

Disintegration time: The film's disintegration period is determined using disintegration machinery stated in official pharmacopoeias. The disintegration time is usually a function of the film composition, because it changes with the formulation, and it typically spans from 5 to 30 seconds. This test is commonly performed using the USP disintegration device. There are no established rules for determining the time it takes for orally rapid disintegrating films to dissolve [29].

***In vitro* dissolution test:** Standard official basket or paddle apparatus are most commonly used to conduct the dissolution tests. During dissolution, sink condition have to be maintained. Film can float over the medium during this operation, makes impossible to execute the test accurately.

Because this problem is more likely to arise with the paddle approach, the basket equipment is most commonly used. 6.8 pH phosphate buffer (300 mL) and 0.1 N HCl were employed as media (900 mL). Conditions like temperature have to be maintained at 37±0.5℃ and speed of revolution to be set at 50 rpm. At predetermined intervals, samples of dissolved medication are collected and analysed using a UV spectrophotometer. Despite its widespread use, dissolving tests are nevertheless prone to significant inaccuracies and tests that fail.

Visual inspection and surface morphology: The colour, homogeneity, and transparency of a prepared or dispersible film can be determined by visual inspection. Surface structure can be investigated by Scanning electron microscopy. The lack of pores and surface homogeneity indicate that the films are of good quality [30].

Surface pH: The pH of a film is commonly determined by placing it on a petri dish, wetting it with distilled water, and then the pH is recorded by contacting the film surface with a pH metre electrode. The pH of the surface must be determined because an acidic or basic pH can irritate the oral mucosa [31].

Moisture uptake and moisture loss: The water absorbing capacity of a film is determined by the percent moisture loss. This metric is usually calculated by first determining the film's initial weight, then placing the film in a desiccator for 3 days. Calcium carbonate is present in the desiccator. Strips are removed after three days and weighed again [32]. Formula for determining the percentage moisture loss is given below.

- **Percentage moisture loss = initial weight−final weight /initial weight x 100**

The moisture uptake in a film is determined by cutting the film into 2 x 2 cm^2 squares. Later, the strips are exposed to conditions of RH 75% at room temperature for a week. The percentage weight gain of the strips is used to calculate moisture uptake.

- **Percentage moisture uptake = Final weight -initial weight /initial weight x 100**

Routes for the administration of thin films:

- **Oral:** The development of polymeric films has improved drug absorption and patient adherence to pharmacological therapy when administered orally, particularly buccal and sublingually. Buccal mucosa has favourable anatomical and physiological properties for drug administration, like presence of smooth muscles with high vascular perfusion, simple accessibility, and bypassing the first-pass metabolism effect. The common site for film delivery to buccal and sublingual mucosa is shown in (Fig. 9). The buccal and sublingual routes are preferred to the other mucosa because they give better drug permeability. The sublingual route is used to transport drugs with high mucosal permeability over the mucosa, and it is used to treat acute illnesses. The buccal route, on the other hand, is favoured to treat the chronic disease when a longer drug release is sought [33].

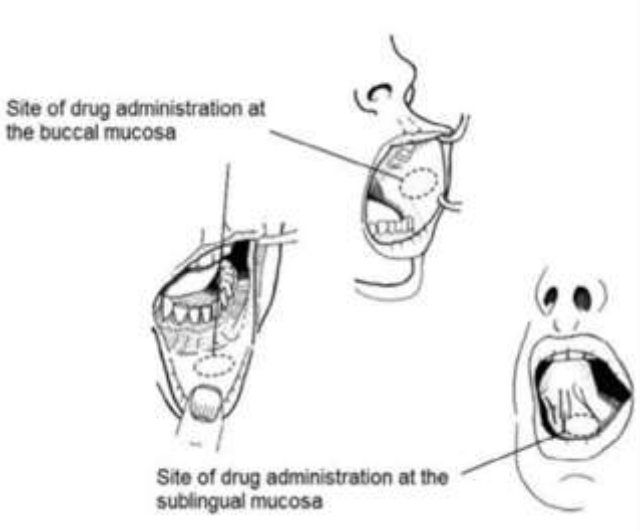

Fig.9. Demonstration of common site for the application of film in buccal and sublingual mucosa

- **Ocular:** Greater than 90% of marketed ocular formulations exists in the form of solutions or suspensions; nevertheless, this traditional dosage form has not shown to be effective in producing promising therapeutic results. To generate a therapeutic response, eye drops must be used often. Patient noncompliance and pulsed administration are the most common outcomes. The ophthalmic film development is popular these days with the goal to increase ocular bioavailability and overcomes the ocular medication delivery hurdles.

- **Transdermal:** Drug-loaded transdermal films are a possible replacement for the current transdermal dosing method. A large range of sustained or controlled delivery systems are prepared by either dissolving or dispersing the drug in the films. For systemic effects, the film forming technique has been used to provide steroidal hormones, analgesics, local anaesthetic, and antiemetic via transdermal distribution [34]. Only a few medications are being developed for transdermal film distribution because various parameters influence drug bioavailability, including molecular size, polarity, pH, skin hydration, drug subcutaneous storage, and drug metabolism by skin flora.

Future perspectives: A drug formulation into number of films has been popular in recent years. Some unwanted disadvantages connected with conventional dosage forms include difficulty of administration; less bioavailability and refusal by the patient led to the evolution of novel polymeric thin films as a drug delivery system. This drug delivery is under scrutiny from both small scale and large-scale pharmaceutical industries. The firms attempt to formulate an extensive collection of thin films for oral, buccal, sublingual, ocular and transdermal routes. So, these polymeric thin films are used as a substitute for the conventional dosage forms which surpasses the disadvantages caused by existing dosage forms. During the formulation and manufacturing processes, the film dosage form faces a number of problems. After transitioning to large-scale manufacturing, such difficulties should be addressed to optimise the overall formulation. As new technologies for preparing thin films are rapidly launched, the future of film technology appears to be bright.

CONCLUSION

Oral fast dissolving films are one among the unique ways in the area of pharmaceutical sciences, as shown in this review. In comparison to traditional dose forms, they have increased patient acceptance and compliance, with absence of risk of choking and improved safety and efficacy. The

main goal of the development of ODFs is to address the difficulties in swallowing traditional oral dose forms in paediatric, geriatric, and mental dysphagia patients.

ODFs have a widespread use in the treatment of high blood pressure, heart burn, allergy, analgesia and other disorders. The major benefits of such dosage forms are their ability to be administered without water usage, which meets the needs of the target demographic for convenience in drug administration while also bypasses hepatic metabolism, results in enhanced therapeutic response.

ACKNOWLEDGEMENTS

The authors are thankful to Sri. K.V. Vishnu Raju, Chairman-Sri Vishnu Educational Society (SVES) and Dr. B. V. Raju Foundation; Dr. Kumar V. S. Nemmani, Director and Dr. K. S. Nataraj, Principal, Shri Vishnu College of Pharmacy (Autonomous), Vishnupur, Bhimavaram, Andhra Pradesh, for providing the required resources and being constant support in bringing out this review work.

REFERENCE

[1] Maniruzzaman M. Pharmaceutical Applications of Hot-Melt Extrusion: Continuous manufacturing, Twin-Screw Granulations, and 3D Printing. *Pharmaceutics*. **2019**; 11(5): 218

[2] Alqahtani MS, Kazi M, Alsenaidy MA, Ahmad MZ. Advances in oral drug delivery. *Front Pharmacol*. **2021**; 12: 618411.

[3] Borges AF, Silva C, Coelho JF, Simões S. Oral films: Current status and future perspectives: I - Galenical development and quality attributes. *J Cont Rel*. **2015**; 206: 1-19.

[4] Sharma D, Kaur D, Verma S, Singh D, Singh M, Singh G, Garg R. Fast dissolving oral films technology: a recent trend for an innovative oral drug delivery system. *Int J Drug Del.* **2015**; 7(2): 60-75.

[5] Kang-Mieler JJ, Rudeen KM, Liu W, Mieler WF. Advances in ocular drug delivery systems. *Eye (Lond)*. **2020**; 34(8): 1371-79.

[6] Castro PM, Fonte P, Sousa F, Madureira AR, Sarmento B, Pintado ME. Oral films as breakthrough tools for oral delivery of proteins/peptides. *J Cont Rel*. **2015**; 211: 63-73.

[7] Irfan M, Rabel S, Bukhtar Q, Qadir MI, Jabeen F, Khan A. Orally disintegrating films: A modern expansion in drug delivery system. *Saudi Pharm J.* **2016**; 24(5): 537-46.

[8] Zhu Y, You X, Huang K, Raza F, Lu X, Chen Y, Dhinakar A, Zhang Y, Kang Y, Wu J, Ge L. Effect of taste masking technology on fast dissolving oral film: dissolution rate and bioavailability. *Nanotechnology***. 2018**; 29(30): 304001.

[9] Momin MM, Dev A. Fast dissolving tablets: a novel approach. *Indian J Pharm Bio Res*. **2015**; 3(1): 18-3.

[10] Amin PM, Gangurde AB, Alai PV. Oral film technology: challenges and future scope for pharmaceutical industry. *Int J Pharm Res.* **2015**; 3(3): 184-203.

[11] Shirvan AR, Bashari A, Hemmatinejad N. New insight into the fabrication of smart mucoadhesive buccal patches as a novel controlled-drug delivery system. *Eur Polymer J*. **2019**; 119: 541-50.

[12] Kaur G, Nagpal D, Nagpal K. Critical Reviews on Paediatric Dosage Form Developments and Medical Devices. *Crit Rev Ther Drug Carrier Syst*. **2020**; 37(6): 553-90.

[13] Sharma D, Kaur D, Verma S, Singh D, Singh M, Singh G, Garg R. Fast dissolving oral films technology: A recent trend for an innovative oral drug delivery system. *Int J Drug Del*. **2015**; 7(2): 60-75.

[14] Russo E, Selmin F, Baldassari S, Gennari CG, Caviglioli G, Cilurzo F, Minghetti P, Parodi B. A focus on mucoadhesive polymers and their application in buccal dosage forms. *J Drug Del Sci Tech*. **2016**; 32: 113-25.

[15] Colombo P. Opinion Paper: Modular Drug Delivery Systems for Personalized Oral Dosage Forms. *Recent Pat Drug Deliv Formul*. **2016**; 10(1): 3.

[16] Kim HM, Woo SJ. Ocular drug delivery to the retina: Current innovations and future perspectives. *Pharmaceutics*. **2021**; 13(1): 108.

[17] Taksande JB, Gupta M, Trivedi RV, Wadher KJ, Umekar MJ. Formulation and characterization of organic-inorganic hybrid film for transdermal drug delivery. *J App Pharm Res*. **2016**; 4(3): 08-15.

[18] L Bruschi M, MB de Francisco L, B Borghi F. An overview of recent patents on composition of mucoadhesive drug delivery systems. *Recent Pat Drug Deliv Formul*. **2015**; 9(1): 79-87.

[19] Jansen EM, Schliephacke R, Breitenbach A, et al. Drug printing by flexographic printing proteins/peptides. *J Cont Rel.* **2015**; 211: 63-73

[20] Sharma D, Kaur D, Verma S, Singh D, Singh M, Singh G, Garg R. Fast dissolving oral films technology: a recent trend for an innovative oral drug delivery system. *Int J Drug Del*. **2015**; 7(2): 60-75.

[21] Pathak, S.D., Goyal, G., Rai, V.K., & Gupta, G. Recent Updates on Orally Disintegrating Thin Films. *J Pharm Sci Res*. **2020**; 12(8): 1131-39

[22] Anbukarasu P, Sauvageau D, Elias A. Tuning the properties of polyhydroxy butyrate films using acetic acid via solvent casting. *Sci Rep*. **2016**; 5(1): 17884.

[23] Amin PM, Gangurde AB, Alai PV. Oral film technology: challenges and future scope for pharmaceutical industry. *Int J Pharm* Res. **2015**; 3(3): 184-203.

[24] Nayak BS, Sourajit S, Palo M, Behera S. Sublingual drug delivery system: a novel approach. *Int J Pharma Drug Anal***. 2017**; 5(10): 399-05.

[25] Russo E, Selmin F, Baldassari S, Gennari CG, Caviglioli G, Cilurzo F, Minghetti P, Parodi B. A focus on mucoadhesive polymers and their application in buccal dosage forms. *J Drug Del Sci Tech.* **2016**; 32: 113-25.

[26] Repka MA, Bandari S, Kallakunta VR, Vo AQ, McFall H, Pimparade MB, et al. Melt extrusion with poorly soluble drugs-an integrated review. *Int J Pharm*. **2018**; 535(1-2): 68-85.

[27] Patil H, Tiwari RV, Repka MA. Hot-melt extrusion: from theory to application in pharmaceutical formulation. *AAPS Pharm SciTech*. **2016**; 17(1): 20-42.

[28] Sharma A, Sri Ganesan P. Formulation development and optimization of fast dissolving film containing carvedilol nanocrystals for improved bioavailability. *J Drug Del Ther.* **2018**; 8(6): 74-1.

[29] Sharma D, Kaur D, Verma S, Singh D, Singh M, Singh G. Fast Dissolving Oral Films Technology: A Recent Trend for An Innovative Oral Drug Delivery System. *Int J Drug Del*. **2015**; 7: 60-75

[30] Padamwar PA and Phasate PP. Formulation and evaluation of fast dissolving oral film of bisoprolol fumarate. *Int J Pharm Sci Res*. **2015**; 6(1): 135-42.

[31] Castán H, Ruiz MA, Clares B, Morales ME. Design, development and characterization of buccal bioadhesive films of Doxepin for treatment of odontalgia. *Drug Deliv*. **2015**; 22(6): 869-76.

[32] Singh CK, Tiwari V, Shankar R, Mishra CP, Jain S, Jain S, et al. A short review on oral fast dissolving film containing cefpodoxime proxetil. *World J Pharm Pharma Sci*. **2015**; 5(1): 1549-77.

[33] Targhotra M, Chauhan MK. An Overview on Various Approaches and Recent Patents on Buccal Drug Delivery Systems. *Curr Pharm Des*. **2020**; 26(39): 5030-39.

[34]. Kouchak M, Rezaee S, Moshabeh N, Handali S. Preparation and evaluation of matrix containing lidocaine and prilocaine for using in transdermal films. *J Rep Pharm Sci*. **2019**; 8(2): 270.