IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
August 2023 Vol.:28, Issue:1

Fast Disintegrating Oral Films – A Novel Drug Delivery System

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An official Publication of Human Journals
ISSN 2349-7203
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Submitted: 25 July 2023
Accepted: 18 August 2023
Published: 30 August 2023

Keywords: Fast disintegrating oral films (FDOFs), patient compliance, rapidly disintegrating, oral mucosa, oral bioavailability

ABSTRACT

Over the past few decades, there has been greater focus on innovative drug delivery systems mainly to improve safety, efficacy, patient compliance and convenience. One such distinct novel drug delivery system that has captured the attention of the pharmaceutical industries is the fast disintegrating oral films (FDOFs). These are thin, stamp-sized dosage forms that can be self-administered without the need of water, rapidly disintegrate, release the drug upon contact with saliva which gets absorbed into blood circulation via GIT. This makes them suitable for pediatrics, geriatrics and patients with dysphagia as they are at a greater risk of choking and find it difficult to swallow capsules and tablets. Fast-disintegrating oral film is prepared by using hydrophilic polymers with suitable excipients. They can be fabricated by different techniques, but the most popular, simple technique is the solvent casting method. The present review provides an insight into FDOFs, their benefits, disadvantages, composition, approaches for formulation and evaluation, its future scope and challenges.

1) INTRODUCTION

The oral route is one of the most preferred routes of drug administration as it is more convenient, cost-effective, and ease of administration lead to high level of patient compliance but it is still challenging route due to swallowing difficulty for pediatric and geriatric patients. It is estimated that 50 % of the population was affected by this problem, which finally results in a higher chance of non-compliance & and ineffective therapy [1]. Oral disintegrating films (ODF) are recently being explored to overcome the problem faced by pediatric and geriatric populations of swallowing the tablets and capsules. Oral disintegrating films when placed on tongue, immediately hydrates by soaking saliva following disintegration infraction of time and/or dissolution releasing active pharmaceutical agent from the dosage form. ODFs are kind of formulations that are commonly prepared using hydrophilic polymers enabling rapid dissolution upon contact with saliva disintegrate in the mouth cavity [2]. Remarkably, after getting swallowed by the patient, they should dissolve and release the drug in the GI tract. This results in enhanced bioavailability and rapid onset of action than conventional dosage form [3].

In recent times, an oral film drug delivery system has gained lots of popularity and acceptance. Oral disintegrating tablets (ODTs) and oral disintegrating films (ODFs) are the typical examples of orally disintegrating drug delivery systems. Recently, fast-disintegrating films are gaining interest as an alternative of fast-disintegrating tablets. The films are designed to dissolve upon contact with a wet surface, such as the tongue, within a few seconds, meaning the consumer can take the product without need for additional liquid [4]. This convenience provides both a marketing advantage and increased patient compliance. A typical ODF is usually equal to the size of a postage stamp. Suitable drug candidates for such systems include cardiovascular agents, neuroleptics, analgesic, anti-allergics and drugs for erectile dysfunction [5].

Anatomy and Physiology of Oral Cavity

The oral cavity is the first portion of the digestive tract which is anteriorly and posteriorly surrounded by lips and fauces respectively. The tongue fills the available space within the mouth. The oral cavity can be divided into two regions.

A. The vestibule: - space between the cheeks and teeth.

B. The oral cavity proper: - the region medial to the teeth [6].

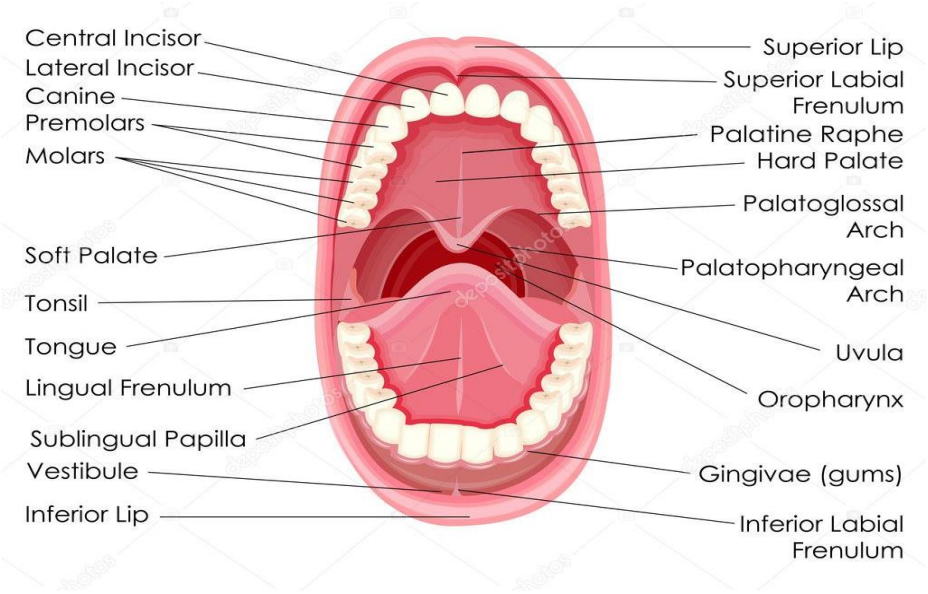

Figure 1: Schematic diagram of oral cavity

Function of Tongue

The tongue is a muscular organ of oral cavity which forms the floor within it. The tongue divided into two categories:

A. The intrinsic muscles (within the tongue) - Responsible for altering their shape and size for speech and swallowing.

B. The extrinsic muscles (outside the tongue) - This moves the tongue from side to side and forward and backward. The tongue moves the food for chewing, shape it into a rounded mass, which is called a bolus and transfers the bolus to the back of the mouth for swallowing. The upper surface and side of the tongue are covered by moist, stratified squamous epithelium [7]. The lingual frenulum is a short fold of mucous membrane which aids in limiting the movements of the tongue posteriorly and in facilitating normal speech. The dorsum of the tongue is divided into two portions by a groove called the terminal sulcus [8]. The papillae on the posterior surface are called “CIRCUMVALLATE PAPILLAE” which contain taste buds and are arranged in an inverted V and 10-12 in number, into each of which open the ducts of minor salivary glands known as the gland of Von Ebner. The whitish conical projections distributed in parallel rows over the anterior two-thirds of the tongue are called “FILIFORM PAPILLAE” which do not contain taste buds [9].

Routes of Drug Transport

There are two main pathways for the passive diffusion of the drug molecule across the membranous tissue.

i. Intracelluler Pathway

ii. Intercellular Pathway

The oral cavity is targeted for a variety of oral disease such as Oral mucositis, Malignant lesions, Apthous stomatitis, Periodontitis and other oral infection. The targeted sites in the oral cavity includes Buccal, Sublingual and Periodontal region. From the membrane of the oral cavity the delivery of drug can be classified into 3 categories [10]:

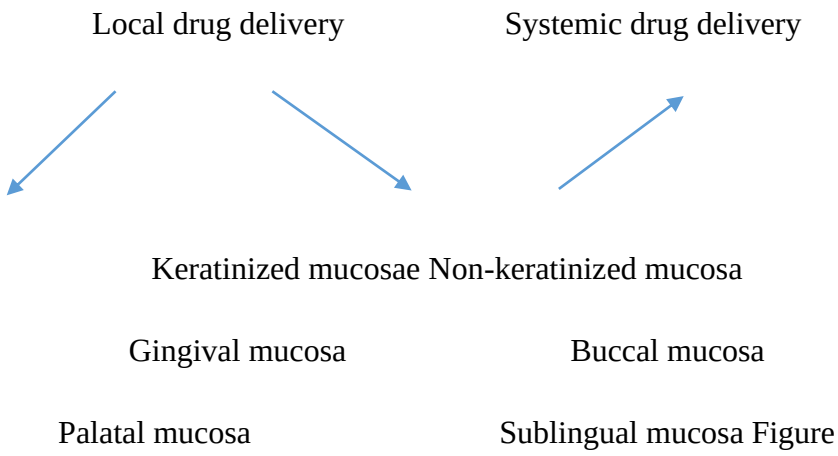

Figure 2: Drug Delivery Via Oral Mucosa

Advantages of FODF's Over Conventional Dosage Form

In market place, the introduction of ODT was strongly associated with counseling of patients about the appropriate administration by giving instructions like ''do not chew/do not swallow''. However, in spite of these instructions, incidents regarding chewing and swallowing were often reported. But, ODFs untied the masses from these adverse events [11]. The administration of ODFs has numerous advantages some of them are as follows:

i. Easy transportation.

ii. Ease of swallowing for geriatrics and pediatrics.

iii. Convenient and accurate dosing.

iv. No need of water for administration.

v. Convenient for dysphasic patients having difficulty in swallowing tablets and capsules.

vi. Rapid onset of action with increased bioavailability due to bypassing hepatic first-pass effect and stability [12], [13], [14].

No expensive lyophilization, high mechanical strength, rapid disintegration, and reduced choking risks are the quality attributes of ODFs. ODFs have attained remarkable significance in the pharmaceutical industry because the reason of possessing unique properties and fast disintegration time ranging from seconds to one minute. ODFs design permits to incorporate a variety of drugs for their pharmacological effects e.g., anti-tussive, anti-epileptic, anti-asthmatic, expectorant, etc. and are some disadvantages of ODFs [15].

Limitations of FODF's

i. High temperature and moisture sensitivity necessitating expensive packaging

ii. the inability of high dose loading

iii. Excessive bitter drugs are not feasible.

iv. Dose uniformity is a technical challenge.

v. Drugs that irritate the oral mucosa cannot be administered by this route [16], [17], [18]

2) COMPONENTS OF AN ORAL FILM FORMULATION

All the ingredients should be generally recommended as safe listed (i.e. GRAS) and should be approved by the FDA for used in oral dosage forms are mentioned below,

1. Active pharmaceutical ingredient (API)
2. Polymer
3. Plasticizer
4. Super disintegrants
5. Sweetening agent
6. Flavoring agent
7. Saliva stimulating agent
8. Coloring agent

9. Cooling agent

10. Stabilizing and thickening agent [19], [20], [21].

1. Active pharmaceutical ingredient

Various classes of drugs can be incorporated into ODFs e.g., anti-histamines, anti-diarrheal, anti-depressants, vasodilators, anti-asthmatic, anti-emetic, etc. The major limitation with Orally disintegrating film is size of the dosage form, hence we can't incorporate high dose of molecule. Basically we incorporate about 25 to 30 mg of Active pharmaceutical ingredient. The Active pharmaceutical ingredient can be milled, micronized, incorporated in form of Nanocrystals depending on the release profile. Most importantly before incorporating Active pharmaceutical ingredient in ODF the taste must needed to be masked of drug. There are some methods available to simplify the mixing technique with enhancing the taste and compressing of bitter taste of Active pharmaceutical ingredients with excipients with good taste is called as Obscuration technique [22].

2. Polymer

There are various polymers used in ODF as an individual or in combination to obtain desirable properties such as Mechanical strength, Drug loading capacity, Drug release and Disintegration time. Depending on the content and type of polymer selected for the preparation of optimized formulation of ODF, which has to be disintegrated within a few seconds after make in contact with mouth. Hence the selection of polymer is most important task in preparation of ODF.

A. Natural Polymers

i. Gelatin: Produced by Hydrolysis or Thermal degradation of collagen and extracted from bones and connective tissue of Bovine source. It has a general sequence of Amino acids coupled with high content of Proline, Hydroxyproline and Glycine. The films are made up of gelatin has low melting point, are biodegradable, edible in nature, non-expensive and has broad application, including food engineering, drug recovery and food packaging.

ii. Chitosan: It is produced by Deacetylation of chitin from crustacean cell. Chitosan are biodegradable polysaccharide with having film forming properties. The films prepared by using chitosan have good biocompatibility, biodegradability, low oxygen permeability and

favorable toxicological properties. The chitosan film has an extended shelf life due to antibacterial and antifungal activity.

iii. Meltodextrins (MDX): MDX prepared by the partial hydrolysis of starch with suitable acids or enzymes. It is a water-soluble biopolymer which contains branched amylopectin, small amount of dextrose and maltase, linear amylase etc. the total reducing powers of all sugars present in hydrolysate material relative to glucose, which is consider as 100 are defined as "Dextrose equivalents" (DE). MDX with low DE reduces cracking and improves flexibility and also has high molecular weight. The solubility and hygroscopicity increases at high DE value but freezing temperature, viscosity and anti-crystalizing power decrease. The DE value effects on the solubility and taste [23], [24], [25].

B. Synthetic Polymers

i. Hydroxy Propyl Methyl Cellulose (HPMC): HPMC is composed of 19-30% of methoxyl group (-OCH3) and 3-12% of hydroxypropyl group (-CH2CHOHCH3), hence they are present in various ratio of both groups substitution, which ultimately affects the mechanical properties, permeability, water solubility and chain length of polymer. The weight % of methoxyl substitution is indicates "Degree of substitution" and the weight % of hydroxyl propyl substitution is indicates "Molar substitution". The grade latters such as E, K, J and F represent the classified degree of substitution and molar substitution. HPMC is insoluble in hot water, acetone, toluene, dehydrated alcohol and soluble in cold water which forms hydrocolloids. HPMC is commonly used as a coating agent, viscosity modifier, film former, excipient which has good biodegradability and biocompatibility [26].

ii. Hydroxy Propyl Cellulose (HPC): HPC is cellulose derivative in which some of the –OH group of the cellulose have been hydroxypropylated to form –OHCH2CHOHCH3 group. HPC has good solubility in cold water and form clear, smooth colloidal solution, and in cold and hot polar organic solution. HPC has a wide range of solubility which help in the selection of the wide range of solvent according to drug solubility. It is insoluble in hot water and deposited as highly swollen floc. HPC is mainly used as binder and coating polymer in preparation of extended-release matrix tablet. It also has good film forming ability, bioadhesion capacity and good carriying capacity with reasonable clarity that is why HPC is used as film forming polymer [27].

iii. Carboxy Methyl Cellulose (CMC) (53-57) CMC is cellulose derivative which is produce when cellulose reacted with sodium monochloroacetate. CMC is cheapest polymer the

biggest reason to most widely used in pharmaceutical industry. It provides ideal system for fast disintegration. Commercially available from degree of substitution range of 0.4 to 1.5. The film forming property is influenced by the degree of substitution value of CMC, because the higher degree of substitution value is directly related to decrease in inner chain reaction. It has ability to carry a wide range of API and produce a film with excellent clarity. CMC has good compatibility with starch and ability to form single-phase polymeric matrix film with enhance mechanical properties. According to some authors the HPMC and CMC are tougher and more elastic in vivo than sodium based film [28].

3. Plasticizer

It reduces brittleness by reducing the glass transition temperature of polymer and helps to improve flexibility. The plasticizer selected on the basis of their compatibility with the polymer and solvent used in formulation. Commonly used plasticizer for ODF preparation.

- Glycerin
- Polyethylene glycol (PEG)
- Propylene glycol (PPG)
- Dimethyl phthalate
- Dibutyl phthalate
- Triacetin
- Citrate ether
- Triethyl citrate.

The plasticizer concentration ranging from 0-20 % used to prevent cracking, peeling and splitting in the ODF. It affects the absorption rate of the drug. The important property of plasticizer to decrease the glass transition temperature of polymer should be ranged from 40-60^{o}C for non-aqueous solvent system and below 75^{o}C for aqueous system. The hydroxyl containing plasticizer like propylene glycol, glycerin, PEG, glycerol, and polyols were easily plasticizer cellulosic hydrophilic polymers. For PVA glycerol is a better plasticizer but diethylene glycol can be used for both PVA and hypromellose films [29], [30].

4. Super disintegrants

When super disintegrants are applied to a formulation, they cause rapid disintegration due to the combined effect of swelling and water absorption. Super disintegrants absorb water and swell, increasing dispersibility and improving disintegration and dissolution. For disintegration, strong interaction with water is necessary. The disintegration mechanism requires swelling, wicking, deformation, or combinations of any [31].

5. Flavor

Flavors are needed to mask the bitter or nauseating taste of the incorporated drug. The amount of flavor depends upon its nature and strength. Any US-FDA-approved flavor can be used such as sweet, sour or mint flavor. One of the research works verified that mint, licorice and sucralose mixture flavors appropriately mask the bitter taste of diclofenac sodium. Electronic tongues are used to discriminate the effect of various taste masking agents (TMAs).

6. Sweetening agents

Sweetening agents are designed to disintegrate or dissolve in the oral cavity. Both artificial and natural sweeteners are used in preparing ODFs. Neotame and Alitame are 2000–8000 times sweeter than sucrose. Fructose has more sweetening power compared to sorbitol and mannitol. Sucralose was found to be 600–1000 times sweeter than sucrose when oral disintegrating films of donepezil were evaluated for taste, after-taste mouth feel. Aspartame and saccharin sodium are likely to be 200 and 300–500 times sweeter compared to sucrose, respectively. It was also reported that sweeteners and flavors have minor effect on flexibility [32].

7. Saliva stimulating agent

Salivary stimulants are generally acidic in nature stimulating the production of saliva in the buccal cavity, consequently, promoting the disintegrating of ODFs. Some commonly used saliva-stimulating agents are citric acid, malic acid, tartaric acid, ascorbic acid and lactic acid.

8. Coloring agents

Pigments are used as coloring agents. Titanium dioxide is most widely used colorant in ODFs and various other pharmaceutical preparations. Apart from titanium dioxide, a full range of colors are available including FD and C, natural and custom Pantone-matched colors.

9. Cooling agents

Cooling agents, such as monomethyl succinate, may be used to increase taste intensity and enhance the product's mouthfeel. Other cooling agents, such as WS3, WS23, and Utracoll II, can be used along with flavors. Monomethyl succinate.

10. Stabilizing and thickening agents

Natural gums, such as xanthan gum, locust bean gum, carrageenan, and cellulosic derivatives, can be used up to 5% by weight. To boost strip properties, other additives such as surfactants and emulsifying agents are added in small amounts [33].

3) PREPARATION METHODS OF ORAL THIN FILMS

Oral Films are prepared using different techniques which include conventional and altered methods for obtaining desired characteristics.

The conventional formulation development methods are as follows:

a) Solvent casting method

b) Semisolid casting method

c) Hot melt extrusion method

d) Solid dispersion method

e) Rolling method

The altered formulation development methods are as follows:

a) Inkjet printing

i. Continuous Inkjet Printing (CIP)

ii. Drop on Demand printing (DOD)

b) Flexographic printing

Conventional Method

Conventional Method

a) Solvent Casting Technique

It is the most popular and widely used technique for the formulation of films. In the solvent-casting process, water-soluble polymers are dissolved in water while the drug and other excipients are dissolved in the proper solvent. The two solutions are then combined and agitated. The air bubbles in this solution are subsequently settled by degassing it under vacuum. Finally, this bubble free solution is cast into a petri plate and allowed to dry. A solvent casting method's crucial steps include casting process, it might occasionally result in films of uneven thickness and erroneous dose due to inappropriate placement on the Petri dish on the oven shelf. OTFs uneven thickness will slow down dispersion since the thicker part of the film takes longer to dissolve. The dissolving time of a film depends on the disintegration time of the film; as the disintegration time of the film grows, so does the dissolving time [34], [35].

Advantages

- Greater thickness, consistency, and more clarity compared to extrusion.
- The films are glossy and free of flaws like die lines.
- Films are more adaptable and have higher physical qualities [36].

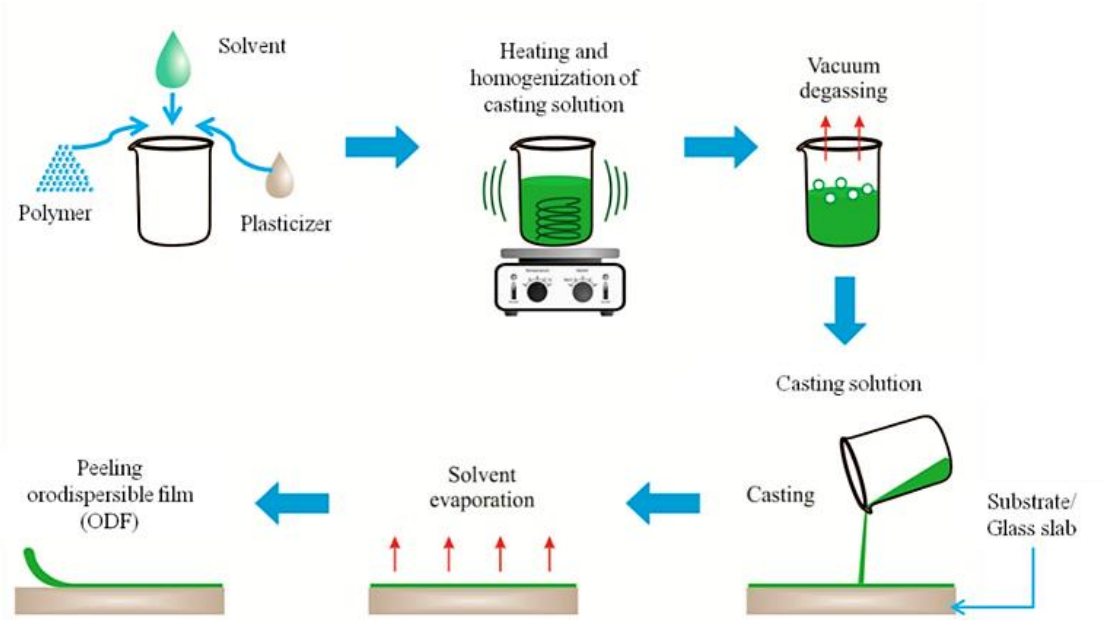

Figure 3: Steps in fabrication of orodispersible films by solvent casting method

b) Semisolid Casting Technique

An acid-insoluble polymer is used as a film constituent; this approach is typically favored. This technique involves creating a water-soluble film-forming polymer solution. The resulting solution is incorporated into the separately created acid-insoluble polymer solution. The two solutions have been suitably blended. After combining the two solutions, the resultant final solution is given a proper dosage of plasticizer to create gel mass. Finally, using heat-controlled drums, the gel mass is cast onto the films or ribbons. The ideal film thickness is between 0.015 and 0.05 mm. The ratio of film-forming polymer to acid-insoluble polymer should be 1:4. The polymers cellulose acetate phthalate and cellulose acetate butyrate are examples of those that are insoluble in acids [37].

c) Hot Melt Extrusion Technique

Since Hot Melt Extrusion (HME) is a continuous, repeatable process that can be automated, it has a variety of uses in the production of pharmaceuticals. Hot-melt extrusion is used to create granules, prolonged-release tablets, transdermal drug delivery systems, and transmucosal drug delivery systems. Temperatures for processing should be 80ºC in the first zone, 115ºC in the second zone, 100ºC in the third zone, and 65ºC in the fourth zone. The granules should be set into the extruder for around 3–4 minutes with the screw speed set at 15 rpm. Plasticizer is gradually introduced. Granulation of the mixture while an anti-sticking agent is present. Overnight, granules are kept and sieved through a 250 um sieve. The

extrusion is fed with dried grains. Processing lasts for 3–4 minutes at the aforementioned temperature. In order to create a 200 um thick film, extrude is pressed at 65ºC.

Advantages

- The bioavailability of poorly soluble drugs is improved.
- Water and solvents are not needed during processing.
- Process that is efficient in terms of costs, manufacturing time, and the number of unit operations.
- There is a homogeneous distribution of small particles.
- Capability for targeted, sustained modification of releases
- Superior stability with a wide range of pH and moisture.
- Among granules of various size ranges, better content uniformity was achieved.

Disadvantages

- Thermal damage is caused by the utilization of high temperatures.
- Processing highly depends on the polymer's flow characteristics.
- There are few polymers available.
- Significant power input is necessary.
- Water or any other volatile solvent must not be present in any excipients.
- A binder with a lower melting point runs the risk of melting or softening while being handled or stored with the agglomerates.
- In particular, for heat-labile materials, higher melting point binders might cause volatility issues because they call for high melting temperatures [38].

d) Solid Dispersion Method

The phrase "solid dispersion" describes the solid dispersion of one or more active substances in an inert carrier when amorphous hydrophilic polymers are present. In order to facilitate easier loading, the active component is diffused into a melted polymer solution. In a suitable liquid solvent that serves as an inert carrier, one or more active compounds may be dissolved.

This happens at 70°C in the presence of an amorphous hydrophilic polymer without the need to drain the liquid solvent in order to achieve the necessary solid dispersion. The dyes are then utilized to create films out of the solid dispersions.

Advantages

- Less processing steps.
- Unconventional techniques.
- Fine particle uniform dispersion is caused by vigorous mixing and agitation.

Disadvantages

Adopting this strategy on a small scale is challenging.

e) Rolling Method

A solution or suspension containing a medication is rolled on a carrier in the rolling method. Mostly water and a combination of water and alcohol are used as the solvent. After drying on the rollers, the film is cut into the necessary shapes and dimensions. little amount of aqueous solvent, other ingredients, including the active substance, are dissolved using a high shear processor. Water-soluble hydrocolloids are dissolved in the liquid to create a homogeneous viscous solution [39], [40].

Altered Methods for the Preparation of OTF [41]

The development of 3D printing technology as a platform for producing pharmaceutical goods has acquired great momentum in recent years. The following benefits over traditional methods of production exist due to the adoption of these technologies for the production of OTFs:

- Accuracy in drug loading, especially when using powerful medications at small doses. Compatibility with a variety of APIs, including proteins, peptides, and those that aren’t very water-soluble.
- The OTF's difficult to attain homogeneity using traditional methods.
- Cost savings result from minimal waste and effective recycling.

Following is a description of two of the main printing methods that many manufacturers and researchers are currently investigating.

a) Inkjet Printing

Digital images given to the computer are turned into 3D objects using the inkjet printing method, which works by hurling drops of ink onto the necessary surfaces. When examining its uses in the pharmaceutical sector, inkjet printing falls into two primary groups. They are as follows,

i. Continuous Inkjet Printing (CIP)

ii. Drop on Demand printing (DOD)

The advantages of inkjet printing are

- A precisely measured small dosage of a potent drug is placed into the films.
- Compatibility with a variety of APIs, including proteins, peptides, and water-insoluble drugs.
- The ODF is homogeneous, which resolves a fundamental problem with traditional techniques.
- Cost savings due to reduced waste and effective reusing.

The disadvantages of inkjet printing are,

- Equipment is pricey.
- High maintenance costs for the machinery.
- Requires personnel who have been properly trained to handle inkjet printing devices.

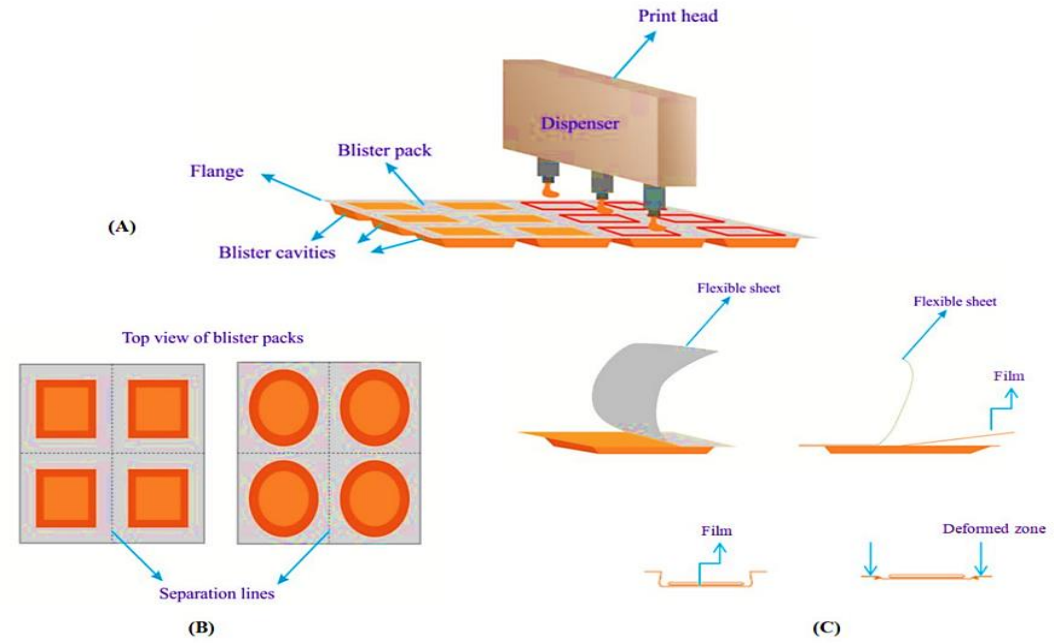

Figure 4: Ink-jet printing: (A) printer head dispensing/printing the drug-containing ink into the blister cavities; (B) top view of the blister packs with inkjet printed ODFs having each dose separated by a separation line; (C) individual packaging unit showing a flexible sheet and the packed film—showing zones of deformity during the opening of the film.

i. Continuous Inkjet Printing (CIP)

In the CIP technique, an ink nozzle consistently ejects ink. By using the appropriate acoustic waves, the ink stream is divided into droplets before it reaches the nozzle. The drops are then exposed to an electric field, which causes them to be deflected until they are in the proper position. The amount of electric field that the drop is exposed to determines the degree of deflection, and as a result, the required pattern is produced. Our intended compositions are left behind when the volatile solvent we utilize vaporizes nearly immediately after the drop lands.

ii. Drop on Demand Printing (DOD)

In DOD printing, the voltages cause the geometry of a piezo-electric substance in the ink chamber to shift, creating a pressure wave in the ink that causes droplets to be produced in numerous nozzles.

b) Flexographic Printing

This particular orienting method utilizes the contact printing theory. It comprises of a fountain roller that transfers the ink, followed by an anilox roller that transfers the ink further and contains the active ingredient in solution or suspension. The amount of ink necessary for a uniform thickness to the plate cylinder holding the polymeric strip is precisely measured by this roller. The ink is printed onto the polymer under pressure. The benefit of this method is that the drug-printed film has already been produced and dried. This prevents the API from losing its activity as a result of heat drying. Averaging 530 oral films per minute, the production efficiency is high. Large print roller manufacturing and a high risk of contamination are downsides of this technology. The optimization and improvement of software for a wide range of drugs and excipients, as well as clinical surveys to evaluate the efficacy, stability, and safety in terms of long- and short-term side effects on patients, are some of the challenges that these techniques, despite being highly innovative, must overcome. The physicochemical or therapeutic qualities of the API must not be altered in any manner by the use of these procedures. The OTF market is expected to grow significantly as a result of the combination of these techniques with conventional processes and subsequent optimization, which is expected to widen the areas of application of these techniques and enable their commercialization more quickly.

The advantages of flexographic printing are,

- Flexographic printing is the method of choice for industrial applications.
- It is possible to precisely load a small quantity of a strong medicine into the films.
- Compatibility with a variety of APIs, including proteins, peptides, and water-insoluble drugs. Produced homogeneously.
- After drying with heat, API's activity is preserved.
- High manufacturing productivity, for instance, this process produces 530 OTFs per minute.

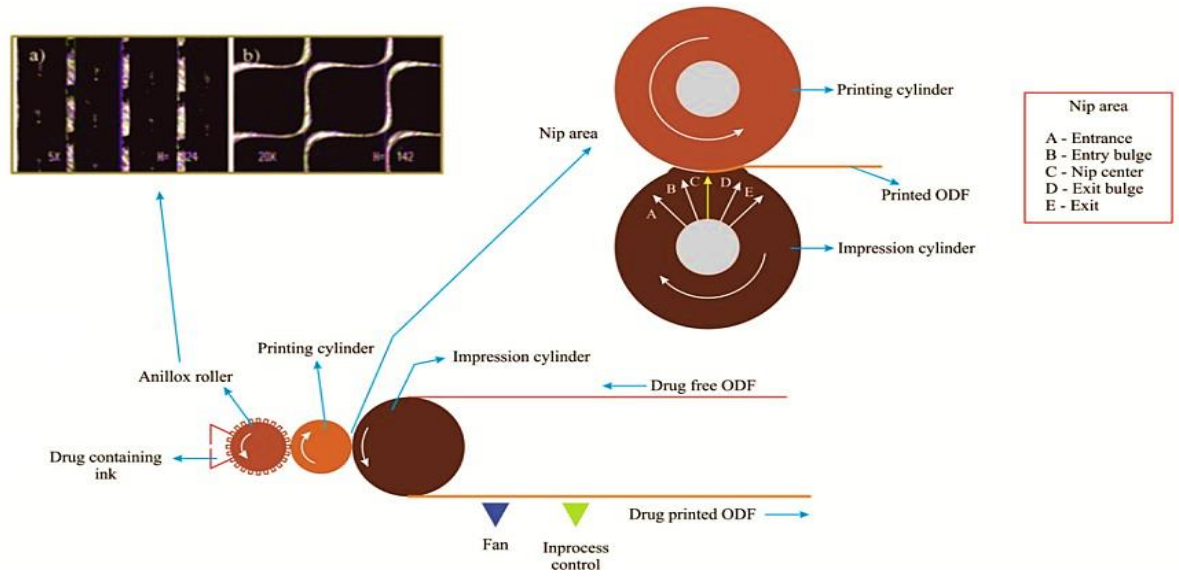

Figure 5: Flexographic printing: flexo process showing micrographs of anilox roller and nip area between the printing cylinder and impression cylinder

The disadvantages of flexographic printing are,

- A big print roller is made during the operation, which carries a significant danger of contamination. For a range of APIs and recipients, software needs to be improved.

3) EVALUATUION PARAMETERS [42]

There are various testing methods applied to evaluate the characteristic features of FODFs. The evaluation methods to assess the quality parameters are described below.

a. Organoleptic Evaluation

Organoleptic evaluation is an in vivo and in vitro taste evaluation approach that is carried out by specialized, regulated human taste panels. In in vitro evaluation, taste evaluation of films is carried out using electronic taste sensor equipment, whereas in vivo evaluation involves human participants. To evaluate the flavors of formulations and the sweetness levels in taste-masking formulations, both in vitro and in vivo approaches are used. Drug development is interested in taste-detecting technology because bad tastes make it harder for elderly, young, and bedridden patients to adhere to their treatment plans.

b. Visual Inspection

The prepared oral films were assessed for flexibility, homogeneity, transparency, and surface roughness.

a. Weight Variation

A weight variation test was performed using 10 pieces of 2 x 1 cm film that were cut from various angles.

b. Film Thickness

This test is necessary to examine the consistency of the film thickness. Three films were chosen at random, and the thickness of each was measured with a typical Vernier caliper. Four corners and the center were used to measure the thickness at five different sites, and the mean thickness was then estimated.

c. Uniformity of Drug Content

The films, each measuring 1 cm2 in area, were put in a glass beaker with 100mL of USP phosphate buffer, pH 6.8, and the mixture was agitated at 100 rpm for an hour. An aliquot of 2 mL was obtained, and it was diluted to 10 mL with USP buffer at pH 6.8 to achieve a theoretical concentration of 8 g/mL. By measuring the absorbance with a UV/VIS spectrophotometer, the drug content was evaluated using a standard curve. The theoretical value was then compared with the actual amount of medication in the patch to measure the percentage of the designated amount.

d. Surface pH of Film

To check for any potential adverse effects in vivo, the pH of the film's surface was measured. It was decided to keep the surface pH as close to neutral as feasible because an acidic or alkaline pH may irritate the buccal mucosa. Films have pH values between 6.4 and 6.98.

e. Flatness

Five longitudinal strips were randomly selected and cut out of a given patch of each formulation to test for flatness. The length of each strip was measured both before and after it was stored at room temperature for 30 minutes. The amount of length variation caused by uneven flatness was calculated as a percentage constriction, with 0% constriction equaling 100% flatness.

f. Folding Endurance Test

Folding endurance measures a film's capacity to endure repeated bending and folding without cracking or breaking. By folding the films repeatedly in the same spot, folding endurance is measured.

g. Percent Moisture Uptake

By preserving the films (2 x 3 cm^2) in an environment chamber with a 400ºC temperature and 75% RH, the percentage of moisture uptake was calculated. The films were removed after a week, weighed, and the percentage moisture uptake was computed in triplicate using the formula below.

$$Percentage\ Moisture\ Uptake = \frac{(Final\ Weight - Initial\ Weight) \times 100}{(\text{Final Weight})}$$

h. *In-vitro* Disintegration test

The film was carefully positioned in the center of a glass petri dish with a diameter of 6.5 cm. There was no tampering with the setup. The amount of time it took the film to totally break down into tiny particles was recorded. Each formulation underwent the test four times, with the mean value being given.

i. *In-vitro* Dissolution test

Dissolution is the rate at which a drug material enters a solution per unit of time under typical temperature, solvent content, and liquid/solid interface circumstances. For dissolution testing, a typical basket or paddle apparatus that is detailed in any of the pharmacopeias can be utilized. It is challenging to conduct a dissolving research of oral film when a paddle-type dissolution device is utilized because they can float above the dissolution medium. The sink conditions and the drug's maximal dose affect the choice of the dissolving medium.

j. Dryness/Tack test

The tenacity with which the strip clings to an accessory, such as a piece of paper that has been placed against the strip, is referred to as tack. There are eight distinct stages in the drying process for films: set-to-touch, dust-free, tack-free, dry-to-touch, dry-hard, dry through (dry to handle), dry-to-recoat, and dry print-free. This test can be carried out using a variety of equipment.

k. Tensile Strength

The point at which the strip specimen breaks is the maximum stress applied to the film. Good tensile strength is necessary for a film. A load failure occurs when a weight causes a film to rupture. The applied load at rupture is multiplied by the strip's cross-sectional area to determine the tensile strength.

l. Swelling Properties

Each film sample is weighed before being placed in pre-weighed stainless steel wire mesh to assess its swelling properties. In a plastic container, 15 ml of medium is added and the mesh containing film is submerged inside. Until a steady weight is to be reached, the increase in film weight is measured at various time intervals. The following equation was used to determine the swelling intensity.

$$\alpha = w_t - w_0 / w_0$$

w_t= weight of film at time t

w_0 = weight of film at time zero

m. FT-IR Studies

Using Fourier Transform Infrared (FTIR) spectroscopy, the compatibility of drugs and polymers was investigated. Shimadzu 160a was used to record the FTIR spectrum between 600 and 4000 cm-1 in Kyoto, Japan using the KBr Disc technique.

n. Scanning Electron Microscopy

To determine surface topography, outer layer morphology, and compositional chemistry, the SEM uses an electron beam.

o. X-Ray Powder Diffraction (XRD)

The powder XRD technique is a vital tool for determining the crystallinity of any substance. To precisely determine the sample's crystallinity, the diffraction angle for analysis was set between 5 and 50 at a scanning speed of 1.2/min.

p. Differential Scanning Calorimetry (DSC)

Utilizing a Discovery DSC 2920 from TA Instruments (New Castle, DE, USA) calibrated with an indium standard, researchers examined the thermal behavior of the pure drug, physical mix, and films. A nitrogen environment was used to heat the aluminum pans from ambient temperature to 200ºC at a heating rate of 10ºC/min while the pure medication, physical mix, and films were precisely weighed (2.0 -0.5 mg).

q. Accelerated Stability Studies

The finalized optimized formulation was kept in a stability chamber for three months at a temperature of 40°C and 75°RH. Every 10 days, a sample was taken out and examined for physical characteristics, in vitro dispersion time, drug content and release.

4) FUTURE SCOPE

In the pharmaceutical industry, great advancements have been made in oral drug delivery technologies. The market has come a long way from conventional tablets/capsules to modern-day fast-disintegrating and rapidly acting tablets/films. Various limitations such as lower bioavailability of oral solid drugs, the inconvenience of administering injections, and inaccurate dosing by liquid formulations are keystone which has turned the focus of pharmaceutical companies to develop novel oral dosage forms that eliminate these limitations [43]. Fast-dissolving oral thin films are designed to meet most of these challenges. The concept isn't new and several over-the-counter oral thin films are readily available. Good acceptance from the users and an increasing demand for over-the-counter oral film products have led to the development of prescription drugs into oral thin films. This emerging area is gaining attention from both established and start-up pharmaceutical firms. Companies are utilizing their oral thin film technologies to develop different types of oral thin films (e.g. oral dispersible, sublingual, buccal). In addition to the drugs, several hormones and vaccines are also being formulated into oral thin films with the aim of providing improved patient compliance [44]. Some of the key players in this area include MonoSol Rx, Applied Pharma Research/Labtec GmbH, BioDelivery Sciences and NAL Pharma. Many companies are collaborating with these technology providers and utilizing oral thin films as a lifecycle management tool for their branded drugs that have lost patents in other dosage forms. There are not many prescriptions for oral thin films currently available in the market; however, the pipeline holds a wider promise. Despite the uncertainties related to the development, approval

and penetration rate, the market is likely to witness stable growth in the coming decade. According to the clinical and regulatory aspects of the US Food and Drug Administration (US FDA), if the product is bioequivalent to that of the existing oral product the drug, an Abbreviated New Drug Application (ANDA) route is followed. There are no clinical studies associated with this generic approval processes (section 505 (j) of the Food, Drug, and Cosmetic Act). An example of such case would be a comparative bioequivalence between an orally disintegrating tablet (ODT) formulation and orally dissolving film (ODF) product. However, developed oral film product may exhibit different pharmacokinetic profile compared to the existing marketed product. The ODF is categorized as a "new dosage form" and the section 505 (b) (2) approval processes needs to be followed. In this case, a new clinical study would be required. The advantage of new clinical study is that it would award 3 years of marketing exclusivity to the product. Preclinical toxicity studies are not required if the molecule is the same as that of the approved product. Safety, tolerability, and efficacy features are to be demonstrated in such trials. Oral mucosa-irritation testing is carried out in both animal models and humans. The future looks very promising for film technology in the time to come as new technologies are rapidly introduced to prepare thin films [45], [46], [47].

Future market potential of OTFs

The future market potential of OTF is huge. For instance, the 'Market Research Future Report', has published a report stating that the Global market for OTFs is positioned to augment at a 'Compound Annual Growth Rate' of 10.50% starting from 2018 to 2023 [106]. Another report from 'Transparency Market Research' reported the global market for OTF is going to be worth of about US $ 15.9 billion by 2024 and will experience a 'Compound Annual Growth Rate' of 9% [48], [49].

5) CHALLENGES

Regarding the methods used in the production of ODFs, those currently used are solvent evaporation and hot extrusion. However, one of the great challenges for the production of oral films is the scale-up, from laboratory to industrial scale, as factors such as heating, mixing speed and temperatures can lead to changes in film quality. Recently, ODFs have been developed as carriers of natural compounds such as vitamins, phenolic compounds, antioxidant, and antimicrobial activity. Thus, it was found that orally disintegrating films are an alternative for the release of active compounds, different from those already existing, which justifies the growing interest in this type of film [50], [51], [52].

6) CONCLUSION

The film technology platform possesses a significant degree of flexibility, which implies promising opportunities for future applications across various delivery routes in the pharmaceutical, biopharmaceutical, and medical markets. Furthermore, this technology offers a chance to enhance revenue life cycles for existing drugs that will soon be susceptible to generic competition upon expiration of their patent. In essence, the utilization of oral films enables efficient life cycle management for products. Despite their apparent simplicity, the manufacturing process and development of oral thin films pose significant challenges in achieving an acceptable product for end-users. Nevertheless, the future market potential for oral thin films is promising and robust. They are poised to become the most attractive dosage forms for all age groups, with the potential to increase patient compliance in all disease conditions.

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