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A REVIEW ON NEW GENERATION ORODISPERSIBLE FILMS AND ITS NOVEL APPROACHES

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ABSTRACT

The oral route is the safest and marketable route for the administration of therapeutic agents for the use of human as well as the veterinary. Pharmaceutical scientists throughout the world are inspecting Orodispersible films (ODFs) as an innovative drug delivery tool. Orodispersible films are now a days are recognized as an alternative approach to conventional dosage form. These thin oral films containing API have ability to releases the drug quickly for both systemic and local action via oral or, sublingual routes. The design of an effective orodispersible film requires an encyclopedic knowledge of pharmaceutical properties of drugs and polymers along with best fit selection of manufacturing process. Hence the motive of this review is to provide an overview of the condemnatory factors that affect the formulation of orodispersible films which includes the physicochemical properties of polymers and drugs, as well as the characterization methods to outwit the difficulties associated with formulation design. It also underlines the latest approaches and trends of the pharmaceutical companies in developing thin film products.

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INTRODUCTION

In the course of the most recent decades, development and imagination have ended up basic aptitudes for making progress. Imagination is the capacity to deliver new and interesting thoughts, one such thought is the advancement of Novel Drug Delivery Systems (NDDS). Among many of the drug delivery system, the orodispersible films are extremely prominent among the pediatrics and geriatrics. Due to their thin size and flexibility they are found to be gaining attention. [1] Orodispersible films are polymeric matrices that meet numerous necessities for being utilized efficiently as a drug release platform. [2] These orodispersible films can be utilized for targeting sensitive site that may not be conceivable with tablets or liquid formulations, hence proving to be a promising candidate for delivery of the drug. [3] Currently, in literature a major quantity of research works and patents are often found, but, still the intensive studies are required to optimize the performance of orodispersible films accurately.

Thin films aren't a recent formulation rather, they had been initially introduced in late 1970 to beat swallowing difficulties as seen in tablets and capsules. Several other names of these thin films have been appeared, for example orodispersible films (ODFs), oral soluble films, mucoadhesive films, oral strips, oral films (oral thin films), buccal films, wafers, ophthalmic films, and transmucosal films. A film that readily dissolves in the oral cavity is generally named as orodispersible film as indicated by European Medicines Agency (EMA) or simply soluble film according to FDA. [3] For the most part, fast dissolving oral films are ultra-thin film (50-150 μm) having size of postage stamp, which dissolves within a few seconds in the oral cavity after being in contact with the saliva leading to fast absorption and instant bioavailability of the drugs. [4][5] Medication stacked in buccal adhesive films are absorbed directly *via* buccal tissue layer that conveys it to the systemic circulation to show its effect. [6] Likewise, wafer is generally specified as paper-thin polymeric film utilized as carriers for pharmaceutical agents. [7]

These orodispersible films have predominance over major drawbacks of rapid disintegrating tablets related to fear of choking, friability and can be utilized for dysphasic and schizophrenic patients. These orodispersible films are specialized in a way that the water is not required for administration because they quickly fragments within a few seconds, discharging the drug in mouth. Orodispersible films, at the point when set on tongue, immediately hydrates by soaking saliva following disintegration and/or dissolution discharging active pharmaceutical agent from the dosage form.[8] No high-cost lyophillisation, high mechanical strength, rapid disintegration, and decreased choking risks are the quality attributes/or hallmarks of ODFs.[9-11] The rationale of possessing distinctive properties and quick disintegration time ranging from seconds to at least one minute have earned exceptional significance in pharmaceutical trade business and patient compliance. ODFs style permits to include a range of medicines for their pharmacological effects e.g., expectorant, anti-tussive, anti-asthmatic, anti-epileptic etc. ODFs drawbacks includes failure of high dose loading, extreme temperature and moisture sensitivity necessitates costly packaging. ODFs are fast disintegrating thin films having an area ranging from 5 to 20 cm^2 in which active pharmaceutical ingredient (API) is consolidated in the form of matrix utilizing hydrophilic polymer. Active pharmaceutical ingredient are often consolidated upto 15 mg in conjunction with other excipients i.e., plasticizers, sweeteners, taste modifiers, colorants etc. The general composition of an ODF is shown in Table I.

Table I: A typical Composition of ODFs. [9]

Components	Concentration (%)
Active Pharmaceutical Ingredient(API)	1-25
Hydrophilic Polymer	40-50
Plasticizer	0-20
Color, Flavor, Filler	0-40

Currently many research on such dosage delivery system can be found in form of patents and other forms but detailed studies for developing the orodispersible films are still to be explored. The abridgement of adapted advice for the quality control and manufacturing of orodispersible films has strived the need for appropriate studies for such drug delivery platform. Hence, this paper will add to give experiences on comprehensive understandings for the formulation and characterization of orodispersible films with the focus on improving their performance from the pharmaceutical standpoint.

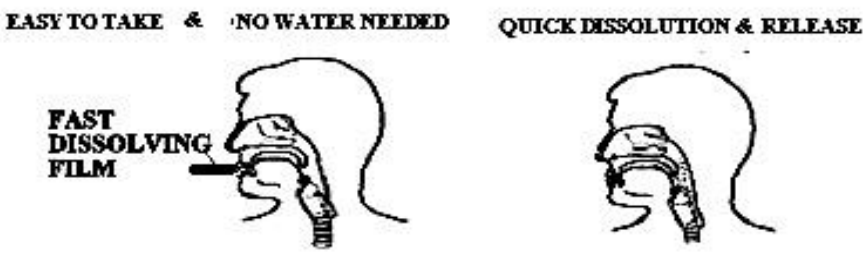

Figure 1: Fast dissolving oral film.

Advantages over conventional dosage forms.[2,12-14]

Oral mucosa is tremendously vascularized, and it provides elevated absorption, expanded bio availability, quicker onset of activity, and overcomes first pass effect. A thin film dissolves rapidly in contrast to other conventional dosage forms.

Table II: Examples of prepared films along with disintegration time.

Prepared Films	Release Characteristics	References
DESIGN AND DEVELOPMENT OF TELMISARTAN FAST DISSOLVING FILM	Here the Disintegration time of all batch was found 24-41 second. For all factorial design batches % Drug content was 86.83- 93.9 %.	[60]
FORMULATION AND EVALUATION OF MOUTH DISSOLVING FILMS CONTAINING TIZANIDINE HYDROCHLORIDE	Here the 100% drug was released within 3 min.	[61]
DEVELOPMENT AND EVALUATION OF ORALLY DISINTEGRATING FILM OF TRAMADOL HYDROCHLORIDE	Here the disintegration time for pullulan films is within 13-17 seconds and for LYCOAT RS 720 the disintegration time was between 19 seconds to 1 min.	[62]
DESIGN AND EVALUATION OF FAST DISSOLVING ORO-DISPERSIBLE FILMS OF METOCLOPRAMIDE HYDROCHLORIDE.	Here the disintegration time for the prepared films using HPMC E5 and SSG ranged from 2.24±1.75 to 3.18±1.87 sec.	[63]

Thin films are less friable and provides ease in carrying dosage form in contrast to commercialized orally rapid disintegrating tablets, which need special packing. Moreover, a unit dose of strip can be carried independently without requiring the secondary holder. It is vital to address the poor stability or instability of liquid dosage forms, particularly the aqueous formulations where attention towards the precise measurement of the amount of medicament and shaking the bottle every time before administration may accord to less acceptance by the patients. Bigger surface area provides better platform for quick disintegration and dissolution thereby releasing the drug in the oral cavity. They impart dosage accuracy and quick release with enhanced patient compliance, and there is no danger of choking. These strips on comparing with oral dissolving tablet possess less fragility and have excellent adhesion. The package ODFs in a blister pack empowers simplicity of transportation and utilization of medication at wherever or time required without water.

Disadvantage of orodispersible films:

• Higher dose cannot be added in these ODFs, which is possible in the case of orally dissolving tablets.
• Longer preservation is troublesome in view of hygroscopic nature and the requirement for specialized packaging.
• Drugs that are not stable at buccal pH cannot be administered.
• Restriction of eating and drinking for quite a while after consuming ODFs.
• Expensive techniques for the preparation of these films in contrast to oral dissolving tablets.

Ideal characteristics of orodispersible films:

- Should possess good mouth feel.
- Should rapidly dissolve in sublingual cavity within seconds
- Not require water to engulf.
- Should not leave any residue in mouth.
- Should evince low sensitivity towards certain environmental conditions like temperature and humidity.

Classification of orodispersible films:

There are three types of oral fast dissolving films:
• Flash release.
• Mucoadhesive melt-away wafer.
• Mucoadhesive sustained release wafers (Table III).

Table III: Classification of oral dissolving film. [15]

Properties	Flash release	Mucoadhesive melt away wafers	Mucoadhesive sustained release wafers
Area (cm^2)	2-8	2-7	2-4
Thickness (microns)	20-70	50-500	50-250
Structure	Single layer	Single or multilayer	Multilayer system
Excipients	Soluble hydrophilic polymers	Soluble hydrophilic polymers	Low/non soluble polymers
Drug phase	Solid solution	Solid solution or suspended drug particle	Suspension or solid solution
Application	Tongue (upper palate)	Gingival or buccal region	Gingiva
Dissolution	60 s	In few minutes forming a gel	Maximum 8-10 h
Site of action	Systemic or local	Systemic or local	Systemic or local

Formulation ingredients

Active Pharmaceutical Ingredient. [16-17]

The rapid dissolving oral film innovation has potential for conveyance of variety of APIs. Since the size of the dosage form is constrained, incorporating high dose of molecules into thin films is challenging task. A typical composition of the orodispersible film contains 1-25% w/w of the drug. Wide variety of APIs can be conveyed through rapid dissolving films such as anti-diarrheal agents (loperamide), anti-asthmatic agents (salbutamol sulphate),cardiovascular, anti-epileptic, antiemetic, analgesics, anti-allergic, anxiolytics, hypnotics, diuretics, anti-parkinsonism agents, and drugs used for erectile dysfunction, anti-Alzheimer's, expectorants, anti-tussive can formulated as film.

Appropriate candidate for ODFs should have following properties:

- Small dose molecules are the best candidates to be incorporated in ODFs.
- Bitter taste of the medication ought to be veiled.
- Should be stable in water and buccal cavity.

Polymers Employed in ODFs

The choice of polymer is an important the most vital and basic parameter for the effective film formulation. The polymers can be used alone or in combination to obtain the desired film properties.

Presently, both natural and synthetic polymers are used for preparation of rapid dissolving oral film. Table IV represents various natural & synthetic polymers which are nowadays used in ODFs preparation.

Table IV: Polymers employed in the preparation of ODFs.

S.No.	Polymer	Examples
1	Natural Polymer	Pullulan, Starch, Gelatin, Pectin,Sodium alginate, Maltodextrins, Polymerized Rosin
2	Synthetic Polymer	Hydroxy propyl methyl cellulose, Sodium Carboxy methyl cellulose, Poly ethylene oxide, Hydroxy propyl cellulose, Poly vinyl pyrrolidone, Poly vinyl alcohol.

Pullulan

Pullulan (Figure-2) is found to be a naturally occurring, fungal polysaccharide produced by liquefied corn starch by *Aureobasidiumpullulans*(originally *Pullulariapullulans*), a ubiquitous yeast-like fungus. It possess a linear structure consisting predominantly of repeating units of maltotriose units, which are comprised of three α–1, 4-linked glucose molecules bonded with a -1,6- glycosidic bonds. Pullulan is stable in aqueous solution over a wide pH range (pH 3-8). Pullulan decomposes upon dry heating and carbonizes at 250-280^{o}C. It dissolves readily in water but is insoluble in organic solvents. [18] Pullulan when dissolved in aqueous solvents tends be viscous but do not form gels. Upon drying, pullulan forms transparent, water-soluble, fat-resistant, odorless, anti-static, flavorless film.

Pullulan has following properties: [19-21]

- ❖ It is impermeable to oxygen and is suitable for protection of readily oxidized fats and vitamins in food. It has been found that pullulan film possess 300 times stronger oxygen barrier than HPMC film and are several times stronger than gelatin film of the same thickness.
- ❖ It can easily be solubilized in cold and hot water to render clear and viscous solution and possess high adhesion and film forming abilities.
- ❖ The main advantages of pullulan are that it is a nonionic polysaccharide and is biodegradable, non-toxic, non-immunogenic, nonmutagenic and non-carcinogenic.
- ❖ Films crafted from pullulan are thermally stable and possess anti-static and elastic properties and can be created into compression moldings.
- ❖ The films crafted from pullulan are non-reducing as well as non-hygroscopic.

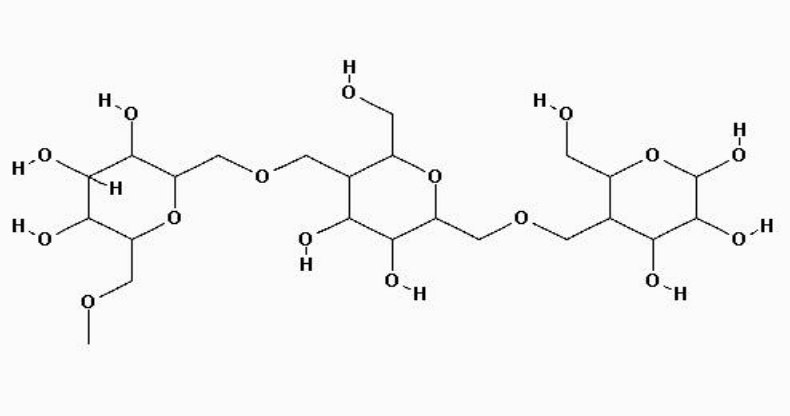

Figure-2 Structure of pullulan.

Starch / Modified Starches

Biopolymer starch is made out of glucose units and possess two main constituents which are, amylose and amylopectin **(Figure-3)**. Amylose moiety is a linear one, having long chain of α-D glucose units bonded together by α-1, 4 glycoside linkages and marginally stretched. It is the amylose which is responsible for the film formation using of starch. [21] Starch can be used to craft films which are biodegradable to partially or fully replace plastic polymer. The films from such polymer are transparent or translucent, tasteless, flavorless and colorless. However, starch film application is restricted due to its efficient barrier against low polarity compound and its poor mechanical strength. Plasticizers are generally required for edible films composed of starch to overcome film brittleness. Usually employed plasticizers for starch films are glycerol and sorbitol. [22]

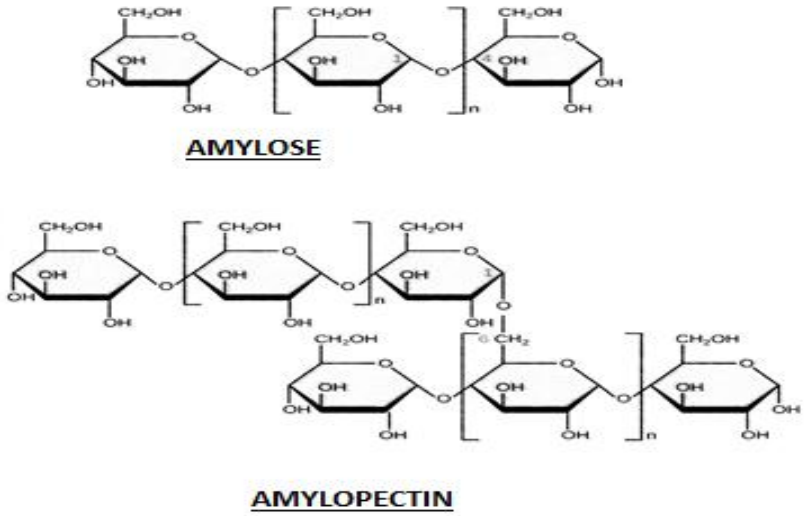

Figure-3: Structure of amylose and amylopectin.

Sodium Alginate

Alginates (Figure-4) are said to be gums, aqueous soluble biopolymers extracted from brown seaweed. Primarily sodium alginate comprises of sodium salt of alginic acid, which is a blend of polyuronic acids made out of residues of D-mannuronic acid and L-guluronic acid. Alginate is an indigestible biomaterial and is obtained from brown seaweeds (belonging to family-*Phaeophyceae*, mainly *Laminaria*). Alginates are found in the cell walls of brown algae as the calcium, magnesium and sodium salts of alginic acid. Edible films composed of alginates are appropriate to load antibacterial compounds along with suitable additives. A blend of starch and alginate is found to produce edible films with improved mechanical properties. [23]

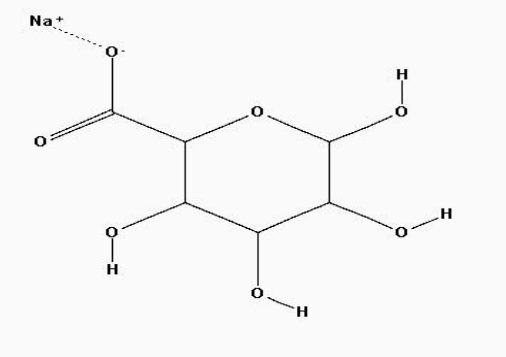

Figure-4: Structure of sodium alginate.

Maltodextrin

Maltodextrin (Figure-5) is a non-sweet nutritious saccharide polymer obtained from partial hydrolysis of starch and is typically found as a creamy-white colored, hygroscopic spray dried powder. Maltodextrin (MDX) comprises of D-glucose units bonded in chains of variable length. The glucose units are basically associated with α (1→4) glycosidic bond. [24] It is easily soluble and gets promptly dispersed in water and slightly soluble to almost insoluble in alcohol. The unique feature about the films crafted from MDX is that these are extremely thin, elegant and is accessible in different shapes and sizes. [25] MDX with a low values of dextrose equivalent (DE) were proposed as film modifiers to tweak the flexibility and reduce the cracking of modified starch-based films. The influence of maltodextrin on modifying the film-forming characteristics of different film-forming polymers, other than lycoat, has been explored by Kunte and Tandale. They investigated the film modifying properties of MDX on hydroxypropylmethyl cellulose (HPMC E6) upon the formulation of taste-masked quick dissolving oral strips of verapamil. [26] Likewise, the film modifying effect of MDX on polyvinyl alcohol (PVA), HPMC and hydroxyethyl cellulose have been investigated in the formulation of a novel tianeptine sodium orodispersible films. [25]

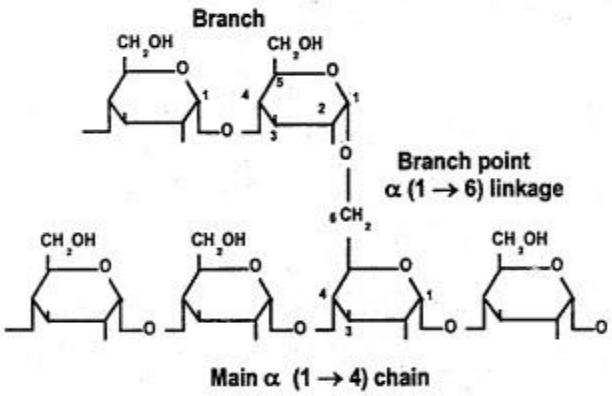

Figure-5: Structure of maltodextrin.

Polymerized Rosin

Rosin (Figure-6) and its esters are accounted to have exceptional film forming properties and can be utilized for enteric coating and delayed release of drugs. [27] Although it occurs naturally but rosin and its derivatives are relied upon to be biodegradable *in-vivo*. Rosin, formerly called colophony or Greek pitch (*Pixgraeca*), is resin which is yellow translucent irregular solid obtained from pines and some other plants, usually conifers. It is obtained by vaporizing the volatile liquid terpene components (Abietic acid) by heating fresh liquid resin and finally producing the polymerized rosin. It has numerous excellent properties, for example, anti-oxidation, high softening point, non-crystallizing and good compatibility with film-forming agent. [28]

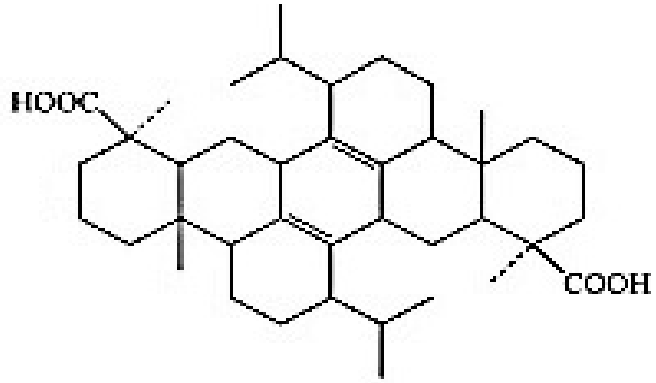

Figure-6: Structure of polymerized rosin.

Chitosan

Chitosan (from chitin) (Figure-7) is significantly versatile and promising biomaterial. It is natural, fungistatic, biodegradable to normal constituents of the body, thus rendering it safe and nontoxic. Products obtained from chitosan are highly viscous, resembling natural gums. Pure chitosan films are generally compact, cohesive and the surface of the films obtained from it has a smooth contour without pores or cracks. Films composed of chitosan such as many polysaccharide based films, tend to show fat and oil resistance and specific penetrability to yet need imperviousness to water transmission. [29]

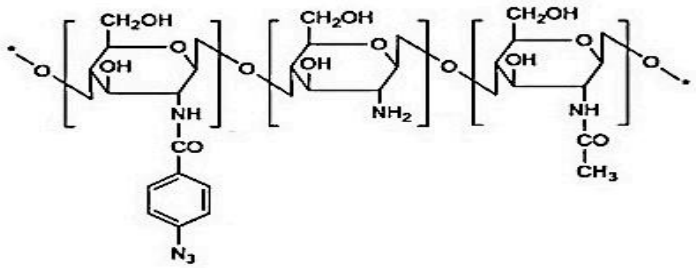

Figure-7: Structure of chitosan.

Hydroxypropyl Methyl Cellulose (HPMC)

Hydroxy propyl methyl cellulose (HPMC) also known as Hyperomellose **(Figure-8)** is a typical excipient commonly utilized as a vital part of orodispersible films, tablet coatings and hard capsule shells etc. The process of developing formulations of HPMC to obtain films that meets the high-quality requirements can be a demanding procedure. Jaime F.C et al., explored the impact of hydration conditions and polymer dispersion on hypromellose (HPMC) film properties, such as clarity, strength, oxygen permeability and water vapor transmission. Its results demonstrated that physical properties of the films were usually unaltered by the range of conditions explored, optical properties were contrarily influenced by high hydration temperatures (50°C). A more direct increment in hydration temperature to 25°C did not influenced optical properties. Also film clarity was not influenced by film thickness, showing that the change in optical properties was a surface effect. [30]

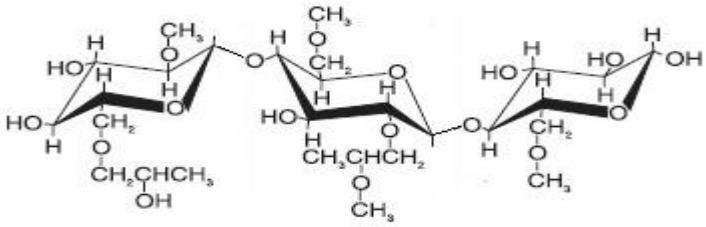

Figure-8: Structure of HPMC.

Hydroxypropyl Cellulose (HPC)

Hydroxypropyl Cellulose (HPC) **(Figure-9)** is a non-ionic water soluble-cellulose ether possessing a versatile combination of properties. Kenji Sugisawa et al., performed research on the applicability and adequacy of HPC in orally disintegrating films by changing the API, excipient and molecular weight of HPC in which the outcomes demonstrated that disintegration time of HPC film tends to be incremented in proportion to film thickness stating that the increasing is dependent on HPC content and the tensile strength was independent. Disintegration time of film was greatly enhanced when formulating Ibuprofen (IBU), which is the most hydrophobic drug tested in their study. Disintegratability of HPC film containing IBU was improved by addition of $CaCO_3$. The film with lower molecular weight HPC (HPC-SSL) demonstrated the quicker disintegration and moderate tensile strength and suggested that ODF could be designed and prepared by using HPC as base material. [31]

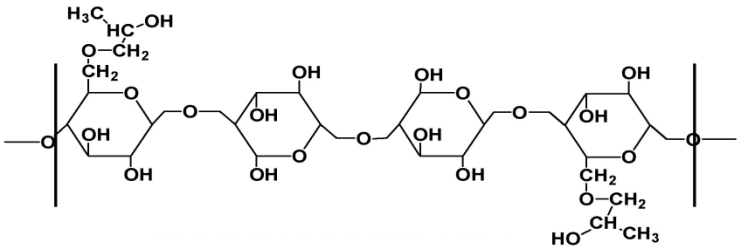

Figure-9: Structure of HPC.

Kollicoat

It is a novel graft copolymer of polyvinyl alcohol-polyethylene glycol **(Figure-10)** that is freely soluble in water. Structurally it consists of 75% polyvinyl alcohol units which is the major component and the remaining 25% consisting the polyethylene glycol units. Films formed from kollicoat are clear, colorless, not tacky, having high pigment binding, immensely flexible and dissolve very quickly in water. Initially it was particularly developed as a coating polymer for instantly release formulations which now has found its usefulness in formulation of orodispersible films. In contrast to pure polyvinyl alcohol films, the flexibility is maintained in storage due to the fact of rearrangement of the molecules to a high level of order ("crystallization") is restricted. Relative humidity in the range of 30–75 % has practically no influence on the mechanical properties of the Kollicoat films. [32]

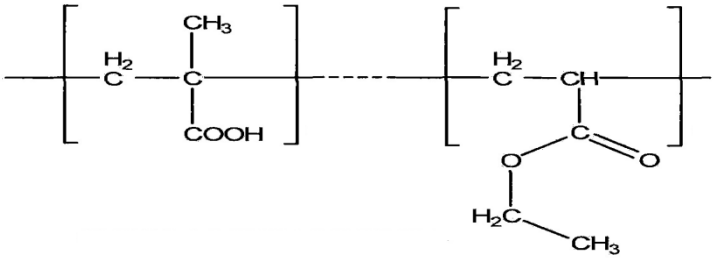

Figure-10: Structure of kollicoat.

Polyvinyl Pyrrolidone (PVP)

Polyvinylpyrrolidone (PVP) (Figure-11), also known by other names such as Polyvidone or Povidone. Among the numerous polymers, the polyvinyl pyrrolidone (PVP) has great film-forming and adhesive behavior on numerous solid substrates and films produced from PVP exhibits the good optical quality and mechanical strength which is necessary for applications. The amorphous structure of PVP additionally provides a low scattering loss, which makes it as a perfect polymer for composite materials for various applications. PVP tends to easily solubilize in water, hence it is preferred to bypass phase separation in the reactions. It has been found that the linking of the ions (especially the alkali ions) with the PVP can prove to be beneficial in preparation of films for their use in electrochemical display devices. [33]

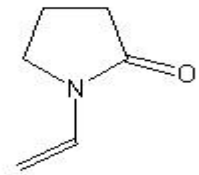

Figure-11: Structure of PVP.

Poly (Ethylene Oxide)

Poly (Ethylene Oxide) (PEO) (Figure-12) is a non-ionic polymer. It has numerous properties such as lubricity, binding, water retention, gelling, and film formation similar to that of other classes of water-soluble polymers. In a study, different grades of Polyox were evaluated for mechanical properties. It was found that the increment in molecular weight causes an increment in mechanical strength rendering it suitable as a film former. It was also found that due to the nature of poly (ethylene oxide) chemistry with lower glass transition temperature (Tg) and more flexibility can be helpful in film forming. The puncture strength of PEO was reported to be much lower than that of cellulose based methyl cellulose (MC) and HPMC polymers. Polyox N-80 has *in-vivo* dissolution time of 23 seconds and *in-vivo* disintegration time of few seconds indicating the results are comparable with the commercially available Listerine films. [34]

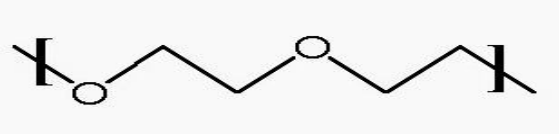

Figure-12: Structure of PEO.

(Image Courtesy: Handbook of Pharmaceutical Excipients by Rowe et.al)

Properties of polymers used

Table V: Properties and Key Findings of Few Polymers Employed on ODFs. [2, 29, 35-37, 56-57]

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. □ 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.	[2, 35, 36, 29]
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 bio adhesive 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.	[2,35,36,37]
Hydroxypropyl cellulose (HPC)	□ White to slightly yellow colored, odorless, inert and tasteless powder. □ Mw 50,000–1,250,000. □ Solubility is found to be in 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.	[2,35,36,37]
Poly (vinyl pyrrolidone) (PVP)	□ Wide range of solubility in various solvents. □ Non-ionic. □ High swelling properties. □Utilized as co-adjuvant to increase mucoadhesion.	□ Mixing of PVP with PVA and HPMC enhances film forming ability. □ Blended with ethyl cellulose and HPC produce films with improved flexibility, softer and tougher properties. □ Different ratios of PVP-alginate mixtures can be utilized for designing controlled release formulations.	[2,35]
Poly (vinyl alcohol)			[2]

(PVA)	White to cream-colored granular powder. Mw 20,000-200,000.	Very flexible films. Mainly used in ophthalmic polymeric preparations.	
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 possess better resistance to tearing, minimal or no curling. Pleasant mouth feeling with no sticky or highly viscous gel formation.	[2,35]
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.	Mixing with sodium alginate and/or CMC, may synergistically improves the properties of the film. Pullulan — HPMC films have enhanced thermal and mechanical properties. 5–25% (w/w) solution forms flexible films. Stable film with less permeability to oxygen.	[2,36]
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 rapid dissolving films, but modified pectin yielded films with rapid dissolution rates. Good film forming capacity at low temperature. Brittle and do not have a clear plastic deformation.	[2,36]
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.	[35 ,37]
Sodium alginate	Occurs as a white or buff powder, which is odorless and tasteless. 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.	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. Rapid swelling and dissolution in water.	[35,37]
Maltodextrin (MDX)	It is a polysaccharide produced from starch by its partial enzymatic hydrolysis. Consists of amylose and amylopectin in different ratios. Possess well fluidity, no particular smell; Low hygroscopicity, less agglomeration, Good carrier for stuffing,sweetening and as aromatizer; Well solubility with proper mucosity.	Use of Maltodextrin is dependent on the grade i.e. the DE (Dextrose Equivalence). Can be used as a carrier for drug entrapment in proniosomal drug delivery. Maltodextrin possessing low DE value has found to impart flexibility with minimum cracking of the films. Maltodextrin with DE value 12 along with 16-20%w/w has been proposed to produce fast dissolving films.	[56, 57]

Plasticizers

Plasticizer is a key ingredient influencing the strength of the orodispersible films. They tends to reduce the brittleness of the strip by lowering glass transition temperature (Tg) of polymers thereby improving the flexibility of the films. The choice of plasticizer will rely upon its compatibility with that of the polymer and also nature of the solvent employed in the casting of the strip. Plasticizer also entrails the air but a good plasticizer is that which entrains air less than 2% only. The flow of polymer will be improved when used along with plasticizer and additionally the strength of the polymer also gets improved. Citrate derivatives which are eco-friendly such as tributyl, acetyl citrate, triacetin and phthalate derivatives like diethyl, dimethyland dibutyl phthalate, are some of the generally employed plasticizer reducing the elastic modulus. Glycerol tends to provide a better plasticizing capacity for films casted utilizing polyvinyl alcohol while diethylene glycol can be employed for both Hypromellose (HPMC) as well as polyvinyl alcohol films. Plasticizers are used normally in the concentration of 0-20% w/w of dry polymer weight. [38]

Sweetening agents

Sweeteners or otherwise nowadays known as sugar substitutes have become the more critical part of the pharmaceutical products proposed to be disintegrated or dissolved in the oral cavity as they tend to increase the acceptability of products. Sweeteners such as sucrose, dextrose, fructose, liquid glucose, glucose and isomaltose are commonly employed additives to impart the good after taste. The sweetening of fructose is perceived rapidly in the mouth when contrasted to sucrose and dextrose. Fructose has found to be sweeter than sorbitol hence prove to be suitable candidate. Also mannitol and isomalt when used combination they additionally provide good cooling sensation and great mouth-feel. Polyhydric alcohols such as Erythritol, Lactitol etc. are less carcinogenic and with reduced amount of calories which is a vital aspect in formulating oral preparations. [36, 39] Sweeteners such as alitame, neotame, dulcin etc. can be incorporated as a sugar substitute.

Saliva stimulating agent

Since dry mouth retards the quick dissolving of films therefore it is necessary to include saliva stimulating agents to escalate the rate of production of saliva that would cause the faster disintegration of the orodispersible strip formulations. Generally those acids which are used in the preparation of food can also be employed as salivary stimulants. Citric acid, lactic acid, ascorbic etc. are few examples of salivary stimulants which are commonly employed. On combination of organic acid and saccharin a synergistic saliva stimulating effect can be produced. Saliva stimulants can either be used alone or in combination between 2 to 5%w/w of the strip. [40]

Conventional approaches for manufacturing of orodispersible films.[41-43]

One or more of the following process can be used to manufacture the mouth dissolving films

1) Solvent casting
2) Semisolid casting
3) Hot melt extrusion
4) Solid dispersion extrusion
5) Rolling methods

Solvent casting method:

Solvent casting is the century old film making process. It is a commonly implemented technique for preparing orodispersible films. This technique is employed to manufacture films of size 2x2 $cm^2$and 3x2 cm^2. Polymers that solubilizes in aqueous solvents are dissolved in suitable vehicle and the drug along with other required additive are dissolved either in aqueous or organic solvent and finally both are mixed and stirred. It is then carefully casted on petridish or plate made up of glass, Teflon or suitable material and dried. Specific types of equipment (Figure-XIV) which is used at large scale production with the appropriate rollers are utilized for pouring the solution on an inert base. Entrapped air is eliminated utilizing vacuum. The final step concludes by drying the films and remove the trace of solvent to obtain the finished product. After the films are dried, the cutting, stripping and packaging is done.

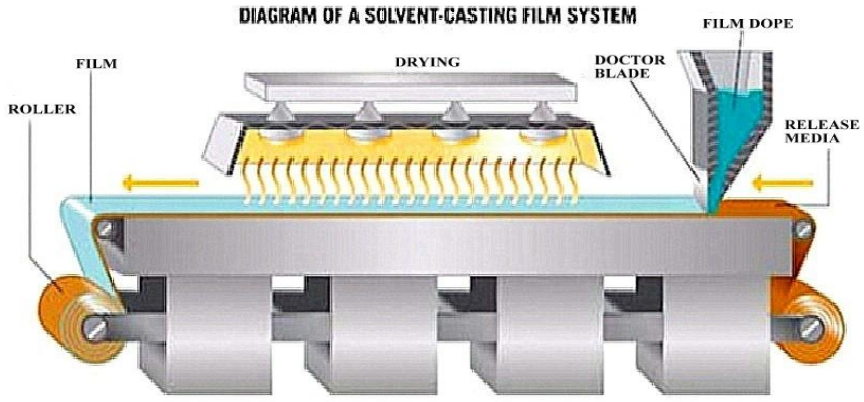

Figure-XIV: Equipment for solvent casting film production.

(Image Courtesy: www.particlesciences.com)

Advantages

• Better uniformity in thickness and better clarity than extrusion technique.
• Films possess fine gloss and freedom from defects such as die lines.
• Films possess more flexibility and better physical properties.

Disadvantages

• The polymer utilized must possess property of solubilization in volatile solvent or water.
• The stable solution with a suitable minimum solid content and viscosity must be formed.
• On the basis of the fluid rheology, sufficient applied mass and required dosage uniformity, the multiple casting techniques are employed.
• Formation of a homogeneous and release of films from the casting support must be possible.

Semi-solid casting method:

Initially a solution of water soluble film forming polymer is prepared. This solution is then further transferred to acid insoluble polymer solution which can be obtained using either cellulose acetate butyrate or cellulose acetate phthalate in sodium or ammonium hydroxide solution in approx. ratio of 1:4. Then carefully plasticizer is added to get a gel mass which is casted into thin films using temperature controlled drums.

Solid dispersion extrusion:

In this technique the immiscible components are extruded along with the drug, and then solid dispersions are prepared. Solid dispersions are shaped in suitable thin sized films with the use of dies.

Advantages

• Lesser processing steps.
• Better uniformity in dispersion of the fine particles due to intense mixing and agitation.

Hot-melt extrusion:

This technique can be employed based on knowledge from the plastics industry where formulators can extrude the combinations of drugs, polymers, and other suitable excipients into desire final forms to achieve appropriate drug-release profiles. In pharmaceutical formulations twin screw extruder has proved to be beneficial due to homogenous and consistent mixing of multiple formulation ingredients leading to improved dissolution rate and bioavailability. The API and other ingredients are mixed in dry state, subjected to the heating process where the mixture gets molten and then extruded out producing thin films. The solvent is completely removed by suitable technique. The produced strips are further cooled and cut to the desired sizes. Employs the usage of instrument as shown in (Figure-XV).

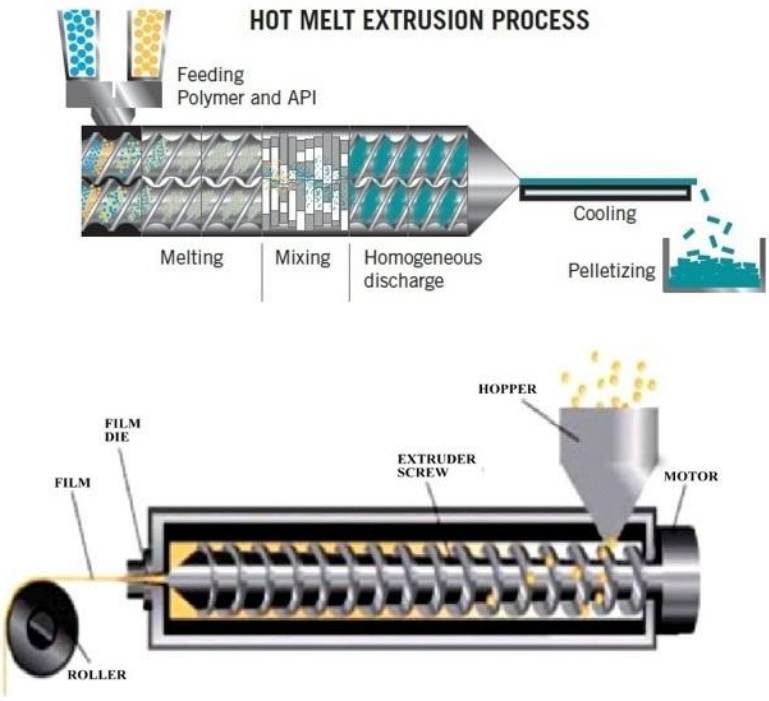

Figure-XV: Hot melt extruder.

(Image Courtesy: www.particlesciences.com)

Advantages

- Need not require the use of solvent or water.
- Cost effective process because it requires less processed time and unit operations.
- Fewer processing steps as compared to any other technique.
- Better uniformity in dispersion of the fine particles because of less intense mixing and agitation.
- Good dispersion mechanism & bioavailability for poorly soluble drugs.
- Less energy in comparison with high shear methods.

Disadvantages

- Thermal degradation may occur due to high temperature.
- Lower melting point binder is not suitable in a situation where melting/softening of the binder can occur during handling and storage of agglomerates.
- Flow properties of the polymers are to be considered before their implementation in dosage form.
- Higher melting point binders needs high melting temperature which adds a problem of volatility particularly for thermolabile materials.

Rolling method:

In this technique suspension or a solution containing drug is rolled on a carrier. The solvent utilized mainly is water or a mixture of water and alcohol. The films are dried on the heated rollers and sliced into desired shapes and sizes. Other ingredients such as API, polymer, plasticizer and other required ingredients are dissolved in a small quantities of aqueous solvent utilizing the high-shear processor.

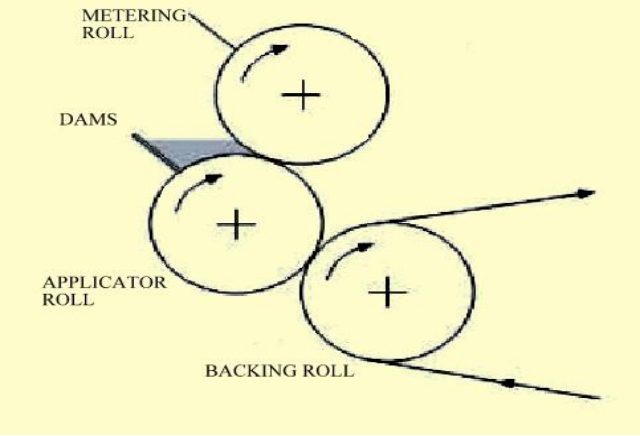

Figure-XVI: A typical rolling machine.

Innovated and Future Technologies Employed in Preparation of ODFs:

Printing Technologies

Novel techniques, for example 3D printing could be utilized for manufacturing polymeric thin films. It could conceivably be a stage for producing the dosage form beneficial to the individual patient. This potentially will resolve the issue of the pharmaceutical industries and pharmacies to meet the future demand of customized medicine. [44] From the perspective of pharmaceutical industry, printing methodologies are usually employed for identifying or labelling of the pharmaceutical dosage forms, especially to streamline the item to be promptly distinguished and to anticipate fake generation. However, this methodology has recently been embraced for the drug loading of pharmaceutical dosage forms. [2] Example in support to such statement is making the use of off-the-shelf consumer inkjet printers which can be utilized for drug-loaded inks and depositing on a polymeric film to yield accurately dosed units of pharmaceutical ingredients. Also, combining the inkjet and flexographic technologies for preparation of films has also been practiced as well in which the inkjet printing is employed for printing of API on different substrate, whereas the flexographic printing was employed for coating of the drug loaded-substrate with a thin film of polymer. [45] Buanz et al. (2011) exhibited the deposition of low doses of an anti-asthmatic drug (salbutamol sulphate) onto commercially available film which were produced from starch using conventional desktop printers. [46] In a study, Janßen et al. (2013) found that it was conceivable to administer tadalafil and rasagiline mesylate solution onto the films composed of hydroxypropyl methylcellulose by utilizing the technique of flexographic printing. The introduction of hydroxypropyl cellulose demonstrated the reduction in drug crystallization after printing. However, the primary drawbacks of flexographic printing technique such as relatively low resolution, greater incidents of contamination and the requirement to prepare a print roller, which is proved to be not suitable for large scale production. [47]

XGel

XGel film Technology produced by BioProgress brought innovation in the product offerings and manufacturing methods to the pharmaceutical industry. X Gel film, potentially leads to the enhancement of the product stability and also has developed polymer film for non-ingestible applications such as sanitary and healthcare devices, cosmetic, ostomy pouches. The active ingredient is accurately dosed and stacked into the body of a premanufactured XGEL™ film, thus avoiding exposure to unnecessary heat and moisture leading to potentially enhanced product stability. [48]

Wafertab

WAFERTAB is a patented drug delivery system that utilizes a unique and potential process to prepare drug-loaded thin films which can be either applied topically or orally conveyed. Wafertab system is itself a great platform to many possibilities for innovative drug design, empowering multiple films with different actives to be bonded together. Active ingredients are incorporated into the film after casting using appropriate polymer. Formulation can be prepared in a numerous shapes and sizes and proved to be an ideal method for delivery of medicines. [48]

Foamburst

In September 2004 a new patent was granted called as FOAMBURST which is for capsules comprised of foamed film. During manufacturing, gas is blown into the film which produces a film with a honeycombed structure or voids in the film which may be gas-filled, empty or loaded with other materials to create particular taste-burst qualities or as a means of conveying active drugs. The light honeycombed structure produces capsules that have tendency to dissolve rapidly and additionally causing a melt-in-the mouth sensation. [48]

Micap

Micap plc consented to an alternative agreement in 2004 to combine its proficiency in micro encapsulation technology along with the Bio Progress (X-gel) water-soluble films. The developments was aimed at providing an innovative drug delivery mechanisms for smoking cessation products (SCPs) which is estimated to achieve $1.4bn in global market. Classes of drugs that can benefit from delivery via this system include hypnotics, anxiolytics, NSAIDs and pain killers, antiemitics in case of nausea and vomiting, 5HT1 agonists for migraine treatment, antiallergics, antacids leading to quick solution in case of acid reflux etc., vitamins and minerals, asthma and treatments for the oral cavity diseases such as pyuria. [48]

Soluleaves

This technique is applied to flavour-release products such as breath mints, confectionery and vitamin products. SOLULEAVES technology provided a novel platform that can be used to convey active ingredients within the oral cavity efficiently and in a pleasant and effortless portable form. SOLULEAVES™ films can also be framed to adhere to the oral mucous membranes which aids in releasing the active ingredient slowly over 15 minutes. [49]

Evaluation Tests: [4, 50-54]

Mechanical Properties

Mechanical properties of film can be defined in terms of thickness, tackiness, tensile strength, and Young's Modulus. It has been reviewed in literature that the soft and weak polymers exhibit low tensile strength, low Young's modulus and low elongation at break whereas, the hard and tough polymer have a high tensile strength, high Young's modulus and high elongation at break.

Thickness test:

A micrometer screw gauge, Vernier's caliper, electronic digital micrometer, or scanning electron microscopy (SEM) images can be employed to measure the strip thickness. It has been seen that the amount of plasticizer is known to increase the thickness of the film slightly. In order to get uniformity of prepared film, thickness is measured at 5 different places. It should be less than 5%.

Tack test:

Tack is the tenacity with which the film adheres to the accessory that has been pressed into contact with strip. This test also determines the dryness.

Tensile strength:

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by formula:

$$\text{Tensile strength} = \frac{\text{Load at failure}}{\text{Strip thickness X Strip width}} \text{X } 100$$

Percentage elongation:

When the sample films are subjected to tensile stress, deformation of the films occurs resulting in stretching or elongation of sample. It is performed to predict the ductility of polymers using a texture analyzer. It is calculated by formula:

$$\%\text{Elongation} = \frac{\text{Increase in length of strip}}{\text{Initial length of strip}} \text{X } 100$$

Young's modulus:

Young's modulus or elastic modulus indicates the stiffness or elasticity of the strip. Deformation of strips can be calculated by plotting the stress strain curve. It is represented as the ratio of applied stress over strain in the region of elastic deformation which can be evaluated using following formula:

$$\text{Young's Modulus} = \frac{\text{Slope}}{\text{Strip thickness X Cross head speed}} \text{X } 100$$

Tear resistance:

Tear resistance of plastic film or sheeting is a complex function of its ultimate resistance to rupture. The maximum stress or force (that is generally found near the Onset of tearing) required to tear the specimen is recorded as the tear resistance value in Newton (or pounds- force).

Folding endurance:

To determine folding endurance, a portion of film is cut and repeatedly folded at the same point till it breaks. The number of times the film could be folded at the same point without breaking indicates the folding endurance value. Typical folding endurance for a film ranges between 100-150.

Organoleptic Evaluation

For evaluating organoleptic properties of the orodispersible films, *in-vitro* methods such as taste sensors and specially designed apparatus are being used. These *in-vitro* taste assessment apparatus are opted for high- throughput taste screening of oral pharmaceutical formulations.

Swelling index:

The studies of swelling index of the films are conducted in simulated salivary fluid at suitable pH. The prepared film is weighed and kept carefully in a pre-weighed stainless steel wire sieve. The sieve containing the film is submerged into 50ml of simulated salivary medium of pH 6.8 held in a mortar. The increase in weight of the film is determined at each time interval until a constant weight is observed. The degree of swelling is evaluated using the formula:

$$\text{SI} = \frac{\text{Wt} - \text{Wo}}{\text{Wo}}$$

Where,
SI = Swelling Index,
Wt. = weight of the film at time "t", and
Wo = weight of the film at t = 0

Surface pH:

Surface pH of the film is determined by placing the film on the surface of 1.5% w/v agar gel and consequently placing a pH paper (pH range 1-11) on film. The change in the color of pH paper is noticed and documented.

Contact Angle:

Contact angle is measured by using Goniometer at room temperature. Place a drop of distilled water on the surface of the dry film. Then the images of water droplet are recorded within 10 sec of deposition with the digital camera. The contact angle is measured on both side of drop and average is taken.

Uniformity of drug content:

This parameter can be dictated by dissolving known weight of film by the process of homogenization in 100 ml of simulated saliva of pH 6.8 for a time period of 30 min with continuous shaking. Content uniformity is then determined by estimating the drug content in individual film. The limit of content uniformity is 85-115%.

Moisture content:

Initially the prepared films are weighed and placed in the desiccators containing cadmium chloride or suitable dessicant. After 3 days the films are reweighed to obtain the percentage of moisture loss which can be calculated using formula:

$$\%\text{Moisture Content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{X } 100$$

Disintegration test:

Disintegrating time is defined as the time (seconds) at which a film breaks when it is brought in contact with water or saliva. The disintegration time limit of 30 s or less for orally disintegrating tablets is described in CDER guidance document which can be applied to ODFs. Pharmacopoeial disintegrating test apparatus may be used for carrying out this study. Typical disintegration time for film is 5-30 s. Different methods which can be approached for determining disintegration time are:

Slide frame method:

In this method the prepared films were clamped into slide frames and are placed planar on a petri dish. Then a drop of distilled water is placed carefully using a pipette onto the oral films. The time until the film dissolved and create a hole within the film was measured.

Petri dish methods:

Simple and convenient method. In this method, 2 mL of distilled water is placed in a petri dish and one film is added on the surface of the water and the time is measured until the oral film was dissolved completely.

In-vitro Dissolution studies:

In these studies cumulative drug release and cumulative percentage of drug retained are calculated. These studies are performed using USP paddle type apparatus. The studies are carried out at 37°C with stirring speed of 75 rpm in 900 ml simulated saliva. Required quantities of samples were withdrawn at predestined time intervals of 2, 4, 6, 8, 10 min and replaced with the same volume of buffer. The samples were collected and the concentration was determined at appropriate wavelength using UV-visible spectrophotometer indicating ascertain dissolution of ODFs.

Packaging [55]

In the pharmaceutical industry it is imperative that the package selected should satisfactorily safeguard the integrity of the product. Specific processing, expensive packaging, and special care are recommended during manufacturing and storage for protection of the dosage of other rapid dissolving dosage forms. For branding purposes and to meet industry regulations, converters may choose to print information directly onto the film unit doses before packaging. Criteria that require special attention includes the need for unit dose packaging, barcode labeling, and the content in guidelines for use, child-resistant seals, and senior-friendly packaging. The material selected must have the following characteristics:

- They must be FDA approved.
- They must protect the preparation from environmental conditions.
- They must meet applicable tamper-resistant requirement.
- They must not be reactive with the material utilized in preparing films.
- They must not bestow to the product tastes or odors.
- They must be non-toxic.

Applications of ODFs in drug delivery system:

- To date, the commercial launch of ODFs is primarily in OTC products inscribing therapeutic categories such as cough/cold, antacid/gas relief, sore throat and mouth fresheners as well as a number of nutritional supplement applications.
- The development of thin strip that dissolves in the mouth for delivery of life-saving rotavirus vaccine to infants can aid in curing the primary source of severe diarrhea and vomiting in children, leading to around 600,000 deaths annually.
- Nausea and Vomiting: Various anti-emetic drugs have been formulated in form of ODFs such as Metoclopromide, Domeperidone, Granisetron etc.
- Transdermal application: The feasibility of active agents such as antimicrobials or analgesics in wound care and other applications could be highly promising approach towards innovation due to its ease of application and better cosmetic appearance. [58]
- Gastroretentive drug delivery: Dispersible films can thought to be a delivery system for poorly soluble molecules and water soluble drugs in film form. The drug can be released by dissolving the film via triggering by pH or enzyme secretion in gastrointestinal tract (GIT) helping in treating GI disorders. [59]
- Asthma: Asthma is a disorder in which patient get attack in which bronchi constricts making it difficult to swallow a solid content. In such condition patient need to take medicine for preventive measure daily the refore dosage form which don't need water and which can be consumed anywhere without water will make it easy for patient. In market, various anti-asthmatic agents in form of tablets, inhalation, injection and syrups are available. Rapid dissolving film have got all advantages of tablets, but in addition to it, it is easy to swallow and preferable for pediatric and geriatric patients (ease of application).It leads to precise dosing, rapid bioavailability, easy application (no need of water), easy to carry. Drugs such as salbutamol, montelukast etc. have successfully been incorporated into ODFs which can serve as a promising drug delivery system for treatment of asthma.

List of some marketed products available as ODFs. (Table VI).

Product	Manufacturer/Distributor	API	Use
Listerine	Pfizer	Cool mint	Mouth fresheners
Triaminic	Novartis	Dextromethorphan HBr	Cough suppressants
Suppress®	InnoZen®, Inc	Menthol	Cough suppressants
Chloraseptic	Prestige	Benzocaine Menthol	Cough suppressants
Gas-X	Novartis	Simethicone	Anti Flatuating
Theraflu	Novartis	Dextromethorphan HBr	Cough suppressants
Ondansetron ODF	Setofilm	Ondansetron	Anti-emitic
Donepezil film	Labtec	Donepezil Hcl	Alzheimer's disease
Klonopin Wafer	Solvay Pharmaceuticals	Clonazepam	Anti- anxiety

CONCLUSION

The formulation of a drug into various types of films has been popular in recent years. This drug delivery platform is being under supervision from both start-up and established pharmaceutical companies. The commercial launch of ODFs was principally in OTC, yet now their utilization has been extended to prescription drugs. The companies strive to design an extensive varieties of thin films for oral, sublingual, ocular, buccal and transdermal routes due to both patient compliance (especially geriatrics and pediatrics). Therefore, as a substitute to conventional dosage forms these polymeric thin films are expected to emerge as a dosage form to overcome the limitations posed by existing dosage forms. Though the use of MDT(Mouth Dissolving Tablets)is popular but then also it has to its credit disadvantages like hygroscopic dosage which may lead to stability issues, grittiness in mouth if not formulated properly, fear of choking, which can be overcomes by ODFs. This drug delivery have tendency to replace the over the counter products from market because of consumer preference also in US, Japan and Europe, the prescription ODFs have now been approved which have potential to dominate over other oral dosage form of same drug. The building success and popularity of ODF's recently in global market makes it indispensable due to its consumer preference. The ODF technology is just in the beginning stage and has bright future because of both patient compliance and pharmaceutical acceptability. Hence this promising drug delivery system needs to be explored more for the benefit of researchers and human being at large.

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None

Conflict Of Interest

The authors declare no conflict of interest.

List of Abbreviations

ODfs : Orodispersible Films
NDDS : Novel Drug Delivery Systems
EMA : European Medicines Agency
API : Active Pharmaceutical Ingredient
S : Seconds
H : Hours
μm : Micrometers
Mm : Millimeters
Mg : Milligrams
mL : Milliliters
HPMC : Hydroxy Propyl Methyl Cellulose
HPC : Hydroxy propyl Cellulose
PEO : Poly Ethylene Oxide
MDX : Maltodextrin
PVP : Poly Vinyl Pyrollidone
Mw : Molecular Weight
η(Greek-Eta): Viscosity
m.Pa.s : Milli Pascal Seconds
Tg : Glass Transition Temperature
DE : Dextrose Equivalent
OTC : Over the Counter

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