REVIEW ON MOUTH DISSOLVING FILMS: AN INNOVATIVE DOSAGE FORM

Ms. Mayuri S. Laware

Department of Pharmaceutics

Amrutvahini College of Pharmacy, Maharashtra, India

Dr. Sadikali F. Sayyad

Department of Pharmaceutics

Amrutvahini College of Pharmacy, Maharashtra, India

ABSTRACT:

Mouth dissolving film is the most superior oral solid dosage form due to its flexibility and alleviation in use. Mouth dissolving films are oral solid dosage form that disintegrate and dissolve inside a minute when positioned in mouth except taking water or chewing. This dosage form permits the medicinal drug to omit the first bypass metabolism so bioavailability of medicinal drug might also be multiplied. Mouth dissolving film has manageable to enhance onset of action decrease the dosing and remove the worry of chocking. There are many strategies had been accessible to prepare the oral films at the buccal cavity. Buccal cavity is one the phase of mouth and it's having a mucosal layer hastily absorbs and distributes the body. This review describes about practice strategies of oral films, determination of polymer for formulation, technologies, and contrast parameters. It in addition offers a brief account of formulation of MDF and problems faced throughout its manufacture.

KEYWORD: Mouth dissolving films, film forming polymers. Bioavailability, Buccal cavity.

INTRODUCTION:

Oral route is most liked and patient-helpful method for drug administration. The greater part of the medications is being taken as tablets and capsules by practically all patients, including grown-up, pediatric and geriatric patients. Be that as it may, around 26 - half of patients find it challenging to swallow tablets and hard gelatin capsules[1]. These patients essentially incorporate,

older (who experience issues taking regular oral dose structures as a result of hand quakes and dysphagia), pediatric patients (who are frequently unfortunate of taking strong oral dose structures, inferable from their immature solid and sensory systems) and others which incorporate the deranged, formatively crippled[2], patients who are uncooperative, on diminished fluid admission designs or sickened, and explorers who might not approach water [3,4.] Furthermore, the moderately unfortunate retention, presence of bountiful stomach related compounds in the GI lumen and epithelium, post absorption efflux (i.e., by P-glycoprotein, and so on), and first-pass digestion by the hepatic catalysts and resulting end, limit the capacity of many medications to arrive at restorative levels by oral course[5]. In addition, a tablet (most normal measurement structure for this course) needs to crumble in the gastrointestinal parcel followed by disintegration of the medication. These cycles stretch out the time until adequacy somewhat, which is unwanted in conditions, for example, torment[5].

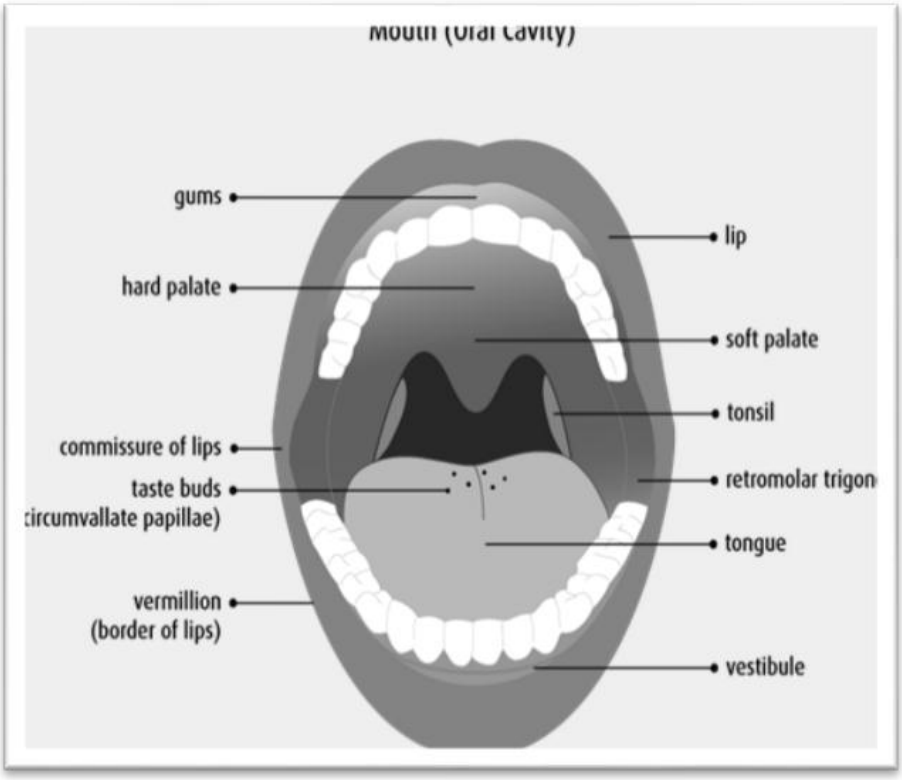

Figure.1: Anatomy of the mouth

Buccal cavity is an attractive and achievable site forsystemic drug delivery as it increases the bioavailability.Bio-adhesion can be described as a phenomenon ofinterfacial attraction forces, in

which two materials areheld together, it occurs between the surfaces of biological, subtract of the natural or synthetic polymers,which allows the polymer to adhere to biological surfacefor an extended period of time as shown in Fig.1.Generally, bio-adhesion is a term that indicates adhesiveinteractions with biological or non-biological derivedsubstances.

Bioadhesive mucosal dosage varieties consisting of adhesive tablets, gels and patches are effects of technological development. Among more than a few dosage forms, the use of polymeric films for delivering medicinal drug into buccal cavity has developed excellent doable in current area. Mouth disintegrating films (MDFs), when positioned on tongue, right away hydrates by means of soaking saliva following disintegration and/or dissolution releasing active pharmaceutical agent from the dosage form. MDFs are variety of formulations which are generally prepared the use of hydrophilic polymers enabling rapid dissolution upon contact with saliva. Oral disintegrating tablets (MDTs) and oral disintegrating films (MDFs) are the common examples of mouthdisintegrating drug delivery systems. These systems had been developed in late 1970 to serve as a choice to conventional dosage forms, for instance, speedy disintegrating pills and tablets for geriatrics and pediatric patients having problem in swallowing traditional dosage forms. A common MDF is typically equal to the size of a postage stamp[6]. In market place, the introduction of MDT was once strongly associated with counseling of sufferers about the excellent administration by way of giving guidance like ‘‘do not chew/do not swallow’’. However, in spite of these instructions, incidents related to chewing and swallowing have been frequently reported. But, MDFs untied the loads from these adverse events.

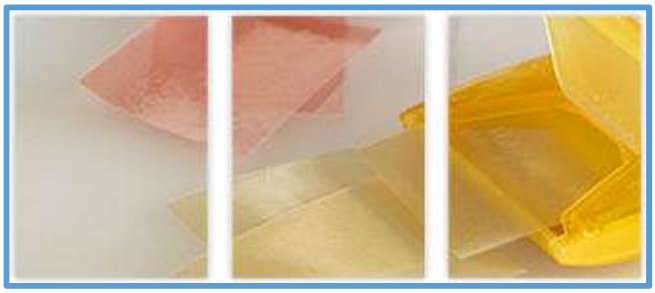

Figure.2: Examples of Film[7]

Oral mouth dissolving film (OMDF) is one such novel strategy to increase customer acceptance by advantage of fast dissolution, self-administration except water or chewing. The film is a best intraoral fast-dissolving drug delivery system, which satisfies the unmet wishes of the market, is convenient to deal with and administer, keeps an easy and convenient packaging, alleviates disagreeable taste, and is easy to manufacture. The film is placed on the top or the flooring of the tongue. It is retained at the site of utility and rapidlyreleases the active agent for local and/or systemic absorption. The development of a fast-dissolving film additionally gives a possibility for a line extension in the market place, a broad range of drugs (e.g., neuroleptics, cardiovascular medications, analgesics, allergy medicines, anti-asthmatic and pills for erectile brokenness) can be viewed as contender for this measurement structure[8,9,10].

Special Features of mouth Dissolving Oral Film

- Ease of administration for patients who are mentally ill-disabled & uncooperative.
- Requires no water; have quick disintegration and dissolution of the dosage form.
- Leaves minimal or no residue in the mouth after administration.
- No risk of choking.
- Provide advantages of liquid medication in the form of solid preparation.
- Amenable and adaptable to existing processing and packaging machinery[11].

Features of Mouth dissolving oral films

This delivery system consists of a thin film structure and dimension like postage stamp. Fast dissolving oral films dissolves in the mouth like a cotton candy leaving pleasant mouth experience and desirable taste. Fast dissolving oral film is unobstructed. After putting it on the top of the tongue, the film dissolves inside seconds, with the aid of passing first omit metabolism as in contrast to pill and different on the spot launch oral solid dosage forms, and may amplify the bioavailability of drug[12,13]. Fast dissolving oral film have to leave minimal or no residue in the mouth after oral administration. Fast dissolving oral film must exhibit low sensitivity to environmental conditions such as temperature and humidity[14,15].

Disadvantages of Fast Dissolving Oral Films

- Drugs which are unsteady at buccal pH can't be controlled.
- Drugs which disturb the mucosa can't be controlled by this course.

- Drug with little portion necessity must be regulated.
- Taste veiling Most medications have unpleasant taste, and need taste covering.
- Unique bundling ODFs are delicate and should be safeguarded from water so it needs exceptional bundling.
- Portion consistency is a specialized test
- Costly bundling of oral film[16].

Table 1: Classification of Oral Films[17]

Property/sub type	**Flash release wafer**	**Mucoadhesive melt-away wafer**	**Mucoadhesive sustained release wafer**
Area (cm2)	2-8	2-7	2-4
Thickness (mm)	20-70	50-500	50-250
Structure	Single layer	Single or multilayer system	Multi-layer system
Excipients	Soluble, highly hydrophilic polymers	Soluble, hydrophilic polymers	Low/non-soluble polymers
Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension and/or solid solution
Application	Tongue (upper palate)	Gingival or buccal Region	Gingival, (other region in the oral cavity)
Dissolution	Maximum 60 seconds	Disintegration in a few minutes, forming gel	Maximum 8-10 hours
Site of action	Systemic or local	Systemic or local	Systemic or local

Formulation aspects for fast dissolving oral films

Formulation of MDOFs involves the intricate application of aesthetic and performance characteristics such as taste masking, fast dissolution, physical appearance, mouth feel etc. From the regulatory perspectives, all excipients used in the formulation of oral film should be Generally Regarded as Safe (i.e.GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms.

Table 2: Composition of mouth dissolving film[18]

S.No	Ingredients	Amount (w/w)
1.	Drug (API)	5-30%
2.	Water soluble polymer	40-50%
3.	Plasticizer	0-10%
4.	Saliva stimulating agents	2-6%
5.	Sweetening agents	3-6%
6.	Surfactant	Q.S
7.	Flavors, colors, Fillers	Q.S

Film forming polymers

Fast dissolving Film is prepared using hydrophilic polymers that swiftly dissolves on the tongue or buccal cavity, handing over the drug to the systemic circulation by way of dissolution when contact with liquid is made. “Water soluble polymers” are used as film formers for quick dissolving films. The water-soluble polymers obtain rapid disintegration, properly mouth sense and mechanical properties to the films. The disintegration of the polymers is lowered through increasing the molecular weight of polymer film bases[19]. Some of the water soluble polymers used as film former areHPMC E3, E5 and E15 and K-3 ; Methyl cellulose A-3, A-6and A-15; Pullulan; carboxmethylcellulosecekol 30;Polyvinylpyrrolidone PVP K-90; Pectin; Gelatin;

SodiumAlginate; Hdroxypropylcellulose; Polyvinyl alcohol;Maltodextrins and Eudragit RD 108, 9, 10, 11, 12 ; EudragitRL100. Polymerized rosin is a novel film forming polymer[20,21].

Ideal properties of the film forming polymers[22]

- The polymer utilized should be non-poisonous, nonirritant and absent any and all leachable debasements.
- It should have great wetting and spread capacity property.
- The polymer should display adequate strip, shear and rigid qualities.
- The polymer should be promptly accessible and should not be over the top expensive.
- It should have great timeframe of realistic usability.
- It shouldn't support cause optional contaminations in the oral mucosa/dental district.
- It should have a decent mouth feel property[23].

Plasticizer

By and large, mechanical properties, for example, elasticity and percent lengthening are improved by adding plasticizer to the plans. The centralization of plasticizer generally goes from 0% to 20% w/w[24].

Sweetening Agent:

Sweeteners have turned into a significant piece of the food items as well as drug items expected to be crumbled or broken up in the oral pit. Regular sugars as well as counterfeit sugars are utilized to work on the acceptability of the mouth dissolving plans. A few reasonable sugars include[24].

Surfactant

Surfactants are utilized as solubilizing or wetting or scattering specialist so the film gets break up in no time and delivery the dynamic specialist immediately. A few quantities of surfactants are utilized in oral strip. One of the main surfactant is poloxamer 407 that is utilized as solublizing, wetting and scattering specialist[25,26,27.]

Table 3: Examples of excipients used in formulation of ODTs[28].

Drug	Polymer	Plasticizer	Sweetener
Nicotine	Pullulan	Glycerol	Dextrose
Nitroglycerine	Hydroxy propyl methyl cellulose	Propylene glycol	Fructose
Zolmitriptan	Poly (acrylic acid) derivatives	Dimethyl phthalate	Glucose
Loratidine	Sodium carboxy methyl cellulose	Diethyl phthalate	Maltose
Loperamide	Hydroxy ethyl cellulose	Dibuyl phthalate	Xylitol
Famotidine	Hyaluronic acid	Tributyl citrate	Maltitol
Flurazepam	Xanthan gum	Trietylcitrate	Mannitol
Acrivastine	Locust bean gum	Acetyl citrate	Sucralose
Dicyclomine	Guar gum	Triacetin	Aspartame
Omeprazole	Carragenan	Castor oil	Alitame
Cetrizine	Sodium alginate	Lanoline alcohol	Neotame
Ezetimibe	Hydroxy propyl methyl cellulose [E5, E6, E15]	Polyethylene glycol 400	Sodium saccharine[29]
Atenelol	HPMC	Glycerine	Aspartane[30]
Venlafaxine hydrochloride	HPMC	Glycerol	Saccharine Sodium[31]
Lornoxicam	HPMC	PEG 400	Aspartame

Blank	Pullulan	PEG 400	Mannitol[32]
Losartan potassium	HPMC	Na–alginate	Saccharin sodium[33]
Fluoxetine	HPMC	Propylene glycol[34]	-
Etoricoxib	Hypromellose (hydroxypropyl methyl cellulose 15 cPs)	Glycerin	Mixed fruit flavour 148691
Paroxetine	Pectin	Glycerol	-
Paroxetine	CMC	PG	-

METHOD OF PREPARATION OF MOUTH DISSOLVING FILM

Fast dissolving films can be prepared by:

1. Solvent casting method
2. Semisolid casting method
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling method

Solvent casting method

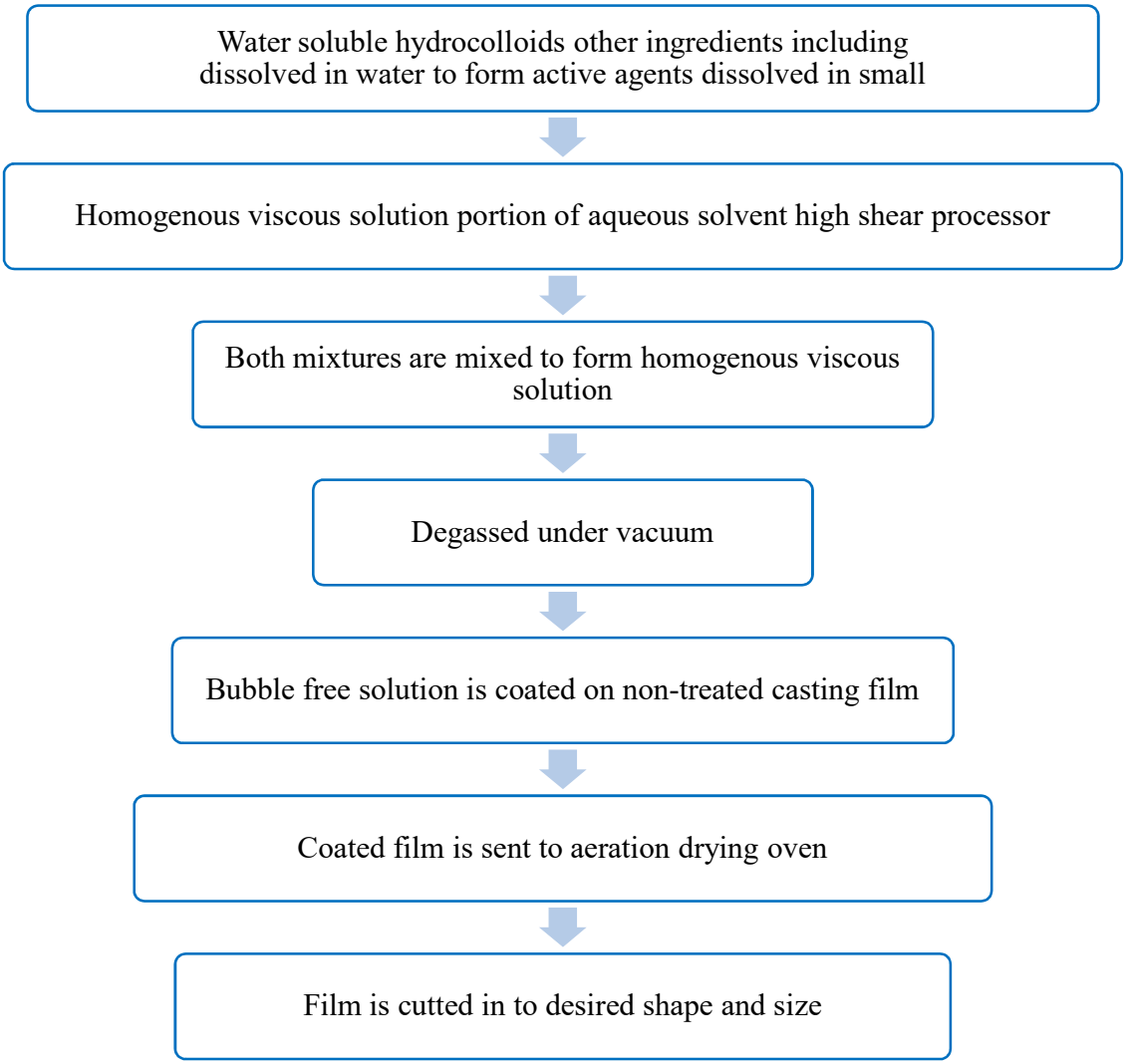

Figure.3: Process of Solvent casting method[35]

Advantage

- Great uniformity of thickness and great clarity than extrusion.
- Films have fine gloss and free from defect such as die lines.
- Films have more flexibility and better physical properties.

Disadvantages

- The polymer must be soluble in a volatile solventor water.

- The stable solution with reasonable minimum solid content and viscosity should be formed

Semisolid casting method

This strategy is ideally embraced when acid insoluble polymers are to be utilized in the readiness of the film.acid excipients are likewise should getting looked at prior to settling a definition. During plan, ensnarement of air pockets can hinder the consistency of arranged films. Accordingly, deaeration of the combination is done with the assistance of a vacuum siphon. Orodispersible film definition of mosapride was additionally effectively ready by utilizing dissolvable projecting strategy [36].

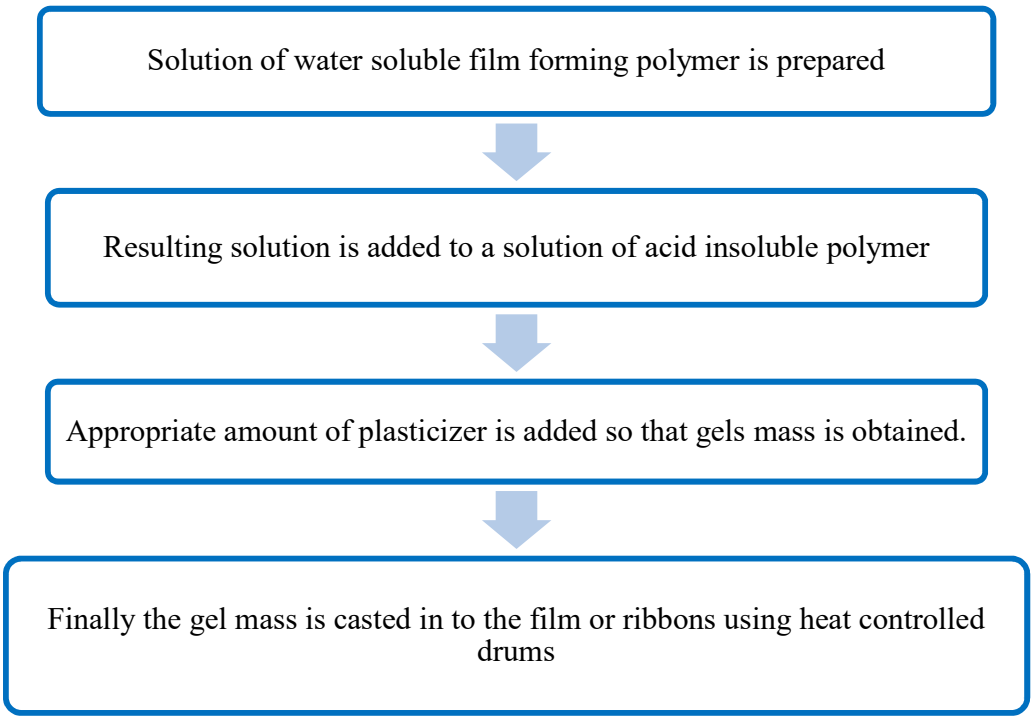

Figure.4: Process of Semisolid casting method

Hot Melt Extrusion:

Hot melt extruder is utilized in this interaction. This procedure includes forming a polymer into a film by means of the warming system. A mix of drug fixings remembering API for dry state is filled in the container, conveyed, blended and exposed to the warming system, and afterward

expelled out in liquid state softened by the extruder. The liquid mass consequently framed is utilized to project the film. A basic advance is the projecting and drying process. This procedure enjoys many benefits, for example, this interaction includes lower temperature and more limited home seasons of the medication transporter blend, unlucky deficiencies of natural solvents, ceaseless activity prospects, least item wastage, great control of working boundaries and potential outcomes to increase [36].

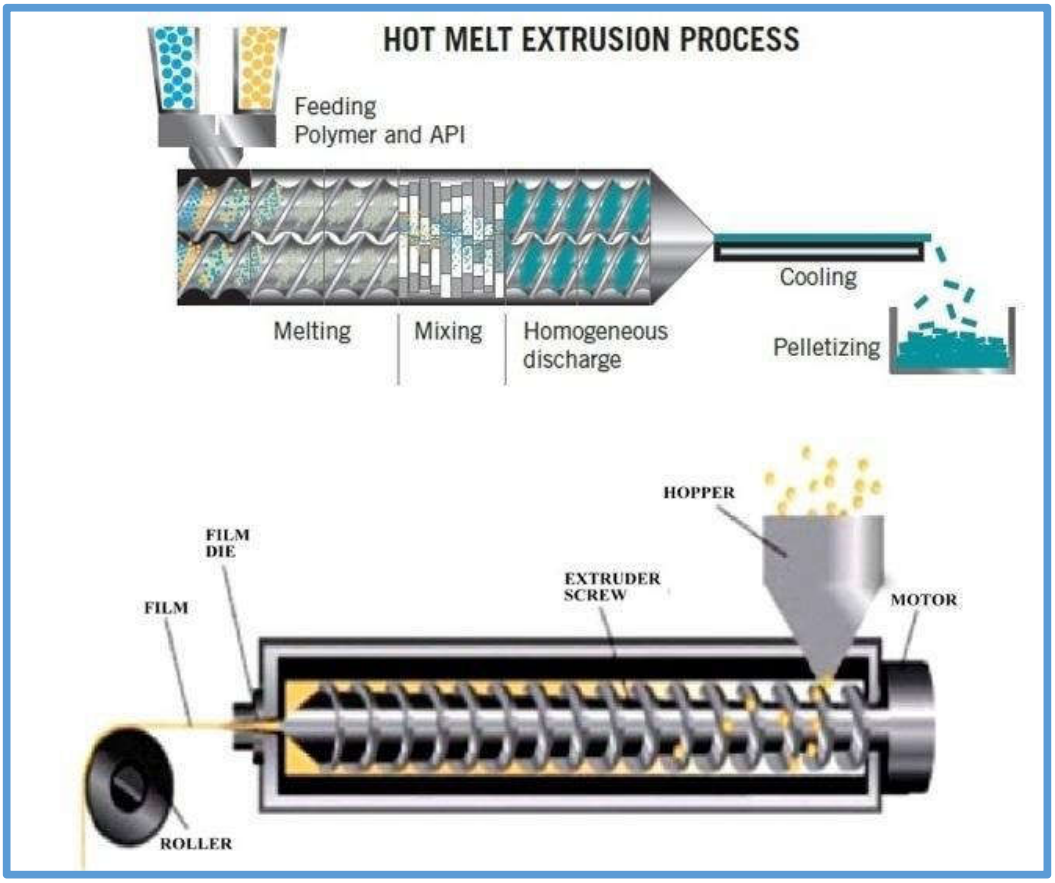

Figure.5: Hot melt extrusion process[24]

Advantages

- No need to use solvent or water.
- Fewer processing steps.
- Compressibility properties of the APT may not be of importance.
- Good dispersion mechanism for poorly soluble drugs.

- More uniform dispersion of the fine particles because of intense mixing and agitation.
- Less energy compared with high shear methods.

Disadvantages

- Thermal process so drug/ polymer stability problem.
- Flow properties of the polymer are essential to processing.
- Limited number of available polymers[36].

Solid dispersion extrusion

The term strong scattering alludes to the scattering of at least one dynamic fixings in a dormant transporter in a strong state within the sight of formless hydrophilic polymers. In this strategy drugs are broken down in appropriate solvents and afterward arrangements are fused into the dissolve of polyethylene glycol underneath 70^{o} C. Then strong scatterings are at long last molded into the film through kicks the bucket[24].

Rolling Method [37,38]

Plot of rolling method is prepared solution should possessspecific rheological properties for rolling onto the drum.Preparation of suspension of drug and polymer in water oralcohol Suspension is subjected to rollers Suspension issubjected to rollers Evaporation of solvent Evaporation ofsolvent.

Feed it through a first metering siphon and control valve to one or the other or both of the first and second blenders. Add expected measure of medication to the ideal blender. Mix the medication with ace group pre-blend to give a uniform lattice. Then a particular measure of uniform lattice is then taken care of to the container through second metering siphons. The film is at long last shaped on the substrate and diverted by means of the help roller. The wet film is then dried utilizing controlled base drying. Dissolvable utilized is fundamentally water and combination of water and liquor.

EVALUATION PARAMETERS

Thickness test:

Thickness of a film is determined by using calibrated digital micrometer and then subsequently mean average is calculated. Generally, three readings from all the batches are determined and average is calculated. Weight variation of a film is calculated in triplicate by cutting the film and determining weight of each film. Uniformity in thickness is important to as certain as it is directly proportional to dose accuracy of the film [39].

Tack test:

Tack is the tenacity with which the film adheresto the accessory that has been pressed into contact withstrip. This test also determines the dryness [6].

Tensile strength:

Tensile strength is defined as maximumstress applied at which the film breaks. Basically, this test isperformed to measure the mechanical strength of films. Itcan be calculated from applied load at rupture divided by thestrip cross-sectional area given in the equation below:

Tensile strength = (Load at breakage/ Strip thickness) × StripWidth

Percentage elongation:

When the sample films aresubjected to tensile stress, deformation of the films occursresulting in stretching or elongation of sample. It isperformed to predict the ductility of polymers using atexture analyzer. It is calculated by formula:

% Elongation = (Increase in length / Original length) ×100

Folding endurance:

To determine folding endurance, aportion of film is cut and repeatedly folded at the same pointtill it breaks. The number of times the film could be folded atthe same point without breaking indicates the foldingendurance value. Typical folding endurance for a film rangesbetween 100- 150[40].

Swelling property:

Reproduced salivation arrangement is utilized to check the enlarging investigations of film. Introductory load of not entirely set in stone and is put in pre weighed tempered steel wire network. This cross section containing film is then dunked into recreated salivation arrangement. Expansion in the heaviness of film is noted at steady pre-decided time stretches until no more expansion in weight. Level of still up in the air by these boundaries:

Degree of swelling = [final weight (wt) – Initial weight (w0)]/Initial weight (w0)

Wt = weight of film at time interval t,

W0 =weight of film attime 0.

Surface pH:

The pH value of a film is usually determined byputting the prepared film in Petri dish and subsequently filmis made wet by using distilled water and noting pH bytouching the film surface with a pH meter electrode.Determination of surface pH is vital as acidic or basic pH isliable to cause oral mucosal irritation[40,41]

Content uniformity:

Items in a film entirely settled by standard examine technique indicated for individual medication in various pharmacopeia. This test is performed on 20 examples utilizing insightful strategies. The acknowledgment worth of the test is under 15% as per Japanese pharmacopeia. As per USP27, the items should go from 85% to 115% with the standard deviation of not exactly or equivalent to 6% Content consistency is turned out for assessing drug contents in individual film [42]

Disintegration time:

Disintegration device referenced in true pharmacopeias is utilized for deciding the crumbling season of a film. Typically, the Disintegration time is the capacity of piece of film as it fluctuates with the definition and for the most part goes from 5 to 30 s. For the most part, he USP deterioration contraption is utilized for this test. There are no authority rules accessible for

deciding crumbling season of orally quick breaking down films. There are two techniques for deciding crumbling season of film [43]

Slide frame method:

A drop of distilled water is pouredonto the film clamped into slide frames placed on petri dish.Time taken by the film to dissolves noted [44]

Petri dish method:

A film is placed into 2 ml distilled watertaken in Petri dish. Time taken by the film to dissolvecompletely is considered as the disintegrating [45]

In-vitro dissolution test:

Standard reputable basket or paddle equipment is used for conducting dissolution studies on films. Sink conditions must be maintained at some stage in dissolution. Sometimes while performing this process, film floats over the medium making it difficult to operate the test properly. This problem is greater probably to appear in case of paddle approach consequently the basket equipment is often preferred. Media used are 6.8 pH phosphate buffer (300 ml) and 0.1 N HCl (900 ml). Temperature is maintained at 37 ± 0.5^0 C and rotation velocity of 50 rpm is commonly adjusted. Samples of drug dissolved are amassed at pre-determined intervals and are analyzed by way of the use of UV-spectrophotometer. Despite its huge use, dissolution test is nevertheless prone to noteworthy inaccuracy and checks let down [46]

Stability Studies:

Stability studies on the optimized oral quick dissolving film is carried out for determination of impact of temperatures and humidity on the steadiness of the drug. The film is saved in an aluminum foil and subjected to steadiness at room temperature. The pattern can withdraw at 3 months and 6 months and subjected for cumulative % drug launch and in vitro dissolution studies to decide disintegration time and disintegration test.

Table 4: Commercial Mouth dissolving film dosage form products[47]

Distributor	API	Strength(mg)
Hughes medical corp.	Methylcobalamin	1
	Diphenhydramine Hcl	2.5
	Dextromethorphan	2.5 – 5.5 – 15
	Folic Acid	1 – 5
	Loratidine	10 – 20
	Caffeine	2.5
Labtec	Donepezil	5-10
	Ondansetron	4-8
Novartis	Dextromethorphan HBr	7.5, 15
	Diphenhydramine HCl	12.5, 25
	Phenylephrine HCl	2.5
	Phenylephrine HCl/ Diphenhydramine HCl	5/12.5, 10/25
	Phenylephrine HCl/ Dextromethorphan HBr	2.5/5, 10/20
	Simethicone	62.5
Pfizer	Diphenhydramine HCl	12.5, 25
	Phenylephrine HCl	10
Innozen	Menthol	2.5

CONCLUSION

Recently pharmaceutical companies embraced fastdissolving films as a practical and accepted alternative totraditional medicines. The special properties of MDFs such as convenient administration, rapidly disintegration, patron preference. The primarythshould behind formulation of MDFs was to cope with the problem in swallowing conventional oral dosage types amongst pediatric, geriatric and psychiatric sufferers with dysphagia. Presently, MDFs are

broadly available for hypertension, acidity, allergy, pain, etc. reflecting their importance. Major benefits of such dosage form are their administration except the use of water satisfying the want of goal populace searching for convenience in drug administration alongside with bypassing the hepatic metabolism, consequently, main to extended therapeutic response.

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