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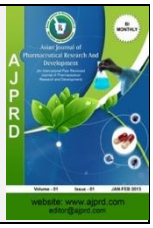

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Review Article

Oral Fast Dissolving Film: A Novel Formulation

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A B S T R A C T

Fast dissolving film is more acceptable and accurate oral dosage form which bypass hepatic system and provide therapeutic effect/response. The pharmaceutical industries prefer this dosage form for patient compliance (for paediatric and geratric patient) and industrial acceptability. Oral film can replace over the counter (OTC) drugs, generic and brand name of the market due tolow cost and consumer's preference. Fast dissolving film when placed in oral cavity gets hydrated quickly, sticks to the site of application and then disintegrates to release the drug. Thus, a fast dissolving film have advantage over other solid oral dosage form. The present review provide an overview about the polymer generally being employed from drug under the BCS Class I to BCS Class IV and factor affecting absorption. For the drug belonging to BCS Class II and BCS Class III, solubility and permeability are the rate limiting step during the formulation of oral fast dissolving film. It further give a brief account about manufacturing method, evaluation, pharmaceutical application and various technology used in oral film formulation.

Keyword- Patient Compliance, Solubility, Permeability, Polymer.

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INTRODUCTION:

Oral route is the most preferred route of administration for the systemic effect. Approximately, 60% of all the formulations are solid dosage form. Tablet is the most preferred dosage form due to ease of transportation, manufacturing and more patient compliance.[1,2]Generally geriatric, pediatric, bedridden, diarrhoe-a, sudden episode of allergic attack, coughing, emetics, emergency(cardiac), patient experience have difficulties in swallowing the conventional oral dosage form. To overcome this problem a novel formulation was developed i.e. oral fast dissolving films. These are also useful for local effect such as local anaesthetic for toothache, oral ulcers, cold sores or coughing.[3]It improve the efficacy of APIs compared to fast dissolving tablets, by dissolving in the oral cavity after the contact with less saliva without chewing and no need of water for administration.[1,4]The delivery system consists of a thin film, which is placed on the patients tongue or mucosal tissue, instantly wet by saliva; the film rapidly dissolves. Then, it rapidly disintegrates and dissolves to release the medication for oral mucosal absorption.[2,5,6]It improve the efficacy of API within minute dissolved in oral cavity after contact with saliva without chewing and no need of water for administration. Fast dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the moisture environment.[2,7]The fast dissolving drug delivery system are specially designed for the drugs which have extensive first pass metabolism and have low dose, for the enhancement ofbioavailability.[2,8]

There are some factors which are taken into consideration

- Drug Lipophilicity.
- Solubility
- pH and pKa of saliva.
- Drug release from theformulation.[9,10]

Overview about FDF:

Fast dissolving films are one among the advance form of solid dosage form due to its flexibility. It is a solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking or chewing.[17,18]FDFs enhanced dissolution rate, better patient compliance and effective therapy.[17,19]It improve efficacy of Acti-ve pharmaceutical ingredient (API) dissolving in the short duration oral cavity after the contact with less amount of saliva as compared to dissolving tablet. Fast Dissolving Drug Delivery Systems was an advance drug delivery system that came into existence in the 1970s and more convenient in use compared to other oral drug delivery system formulation, like tablets, syrups, capsules. FDDS have major benefit over other conventional dosage forms as the formulation gets rapidly disintegrated and dissolves in the saliva without need of water and release the drug to desired response on desired site of action.[2,11] The most popular oral solid dosage forms are tablets and capsules. Many patients particularly pediatric and geriatric patients find difficult to swallow tablets and hard gelatin capsules and do not take their medicines as prescribed. Difficulty in swallowing (dysphagia) is seen to afflict nearly 35% of the general population. In some conditions, like, motion sickness, sudden episode of allergic attack, fear of choking, coughing and unavailability of water, the swallowing of tablet or capsules may become difficult. To overcome these difficulties, several fast dissolving drug delivery systems have been developed.[2,12]To eliminate the drawbacks of fast dissolving tablet a fast dissolving film can be placed. Fast dissolving films (FDF) are similar to fine/thin strip of postage stamp in their shape, size and thickness. Fast dissolving film is placed over the patients tongue or oral mucosal tissue, instantly get wet by saliva, the film rapidly hydrates and adheres to the site of application. It get rapidly disintegrates and dissolves to release the medication for oromucosal absorption. Fast dissolving drug delivery system (FDDS) is suitable for drugs which undergo high first pass metabolism and is used for improving bioavailability with reducing dosing frequency to mouth plasma peak levels, which in turn minimize adverse effects and also make it cost effective.[2, 13]Drug delivery by per-oral administration arise some problems such as hepatic first pass metabolism and enzymatic degradation within the GItract.[2,14]

The ideal characteristics of a drug to be selected

- The drug should have pleasant taste. In case of bitter taste, Taste masking agent are used.
- The drug should have dose up to 40mg.
- The drugs have smaller and moderate molecular weights are preferable.
- The drug should have stability and solubility in water and saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosaltissue.[15]

Advantage[20]

- It can be taken without water.
- It disintegrate/dissolve quickly in mouth.
- It should be flexible and light in weight.
- It is appropriate to all age group.
- Appropriate for patients who are ill or uncooperative.
- Films remain stable for longer time as it is in solid dosage form.
- The drug absorbed directly from film formulation into the blood, so it avoids undergoing of first pass hepatic metabolism which seen in conventional dosage forms
- Rapid disintegration of film give fast onset of action; thus, it enriches safety and efficacy profile of active pharmaceutical ingredient (API).

Disadvantage[20]

- Drug give action in high doses cannot be incorporated into films.
- Maintaining dose uniformity is challenging task for films.
- Moisture sensitivity.
- Require special packaging.
- API which are unstable at pH of the saliva cannot be designed in the form of film.

Table: 1 Composition of fast dissolving films[1]

S. No	Ingredients	Quantity	Examples
1.	Active Pharmaceutical Ingredient	1-25%	Salbutamol, Omeprazole, Paracetamol, Meloxicam, Valdecoxib etc
2.	Film Forming Polymer	40-50%	HPMC E3, E5, E15, K-3 , Methyl Cellulose A-3, A-6, A-15, Pullulan, CMC, PVP, PVA, HPC etc.
3.	Plasticizer	0-20%	Di butylpthalate, Glyerol, PEG, etc
4.	Surfactant (solubilizing, dispersing, wetting agent)	q.s.	SLS, Tween, Polaxamer, Benzalkonium chloride etc.
5.	Saliva stimulating agent	2-6%	Citric acid, malic acid, tartaric acid, ascorbic acid etc.
6.	Sweetening Agent	3-6%	Sucrose, isomaltose, sucralose,
7.	Flavouring Agent	10%	US FDA approved like mint, sour , fruit flavors etc.
8.	Colouring Agent	1%	FD and C, EU color, natural colour etc.

Biopharmaceutical Classification Systems (BCS)

I. BCS Class I Drug

Drug belong to this class have high absorption and high permeability profile. There is no need of improving any parameter as there is no rate limiting step for this class drug.

II. BCS Class II Drug

Drugs belong this class have high absorption and low dissolution. The absorption/ bioavailability are limited by dissolution rate. These drugs exhibit varying bioavailability and small increment in dissolution may hence result in substantial improvement in bioavailability. Hence, solubility enhancement is the factor taken into consideration for formulating BCS class II drugs. For increasing dissolution of drug, solubility enhancement agents are used.

i. β-Cyclodextrin

β-Cyclodextrin is cyclic oligosaccharides, consist of 7 glucose subunit joined by alpha 1,4 glycosidic bonds. Cyclodextrin are produced from starch by enzymatic conversion. The complex product of cyclodextrins with hydrophobic molecules make it able to penetrate/cross body tissues, these complex product is used to release biological active compounds under specific conditions. β-Cyclodextrin also enhance mucosal penetration of drug. Inclusion complex was prepared by kneading method. Concentrations of drug and β-Cyclodextrin are in ratio 1:1 to 1:4.

ii. PEG

PEG is used as biodegradable polymer. It also enhance the aqueous solubility of poorly soluble drug using solid dispersion technique. Inclusion complex were prepared by fusion or melting method. Concentrations of drug and PEG are in ratio 1:1 to 1:3.

iii. Poloxamer188

Poloxamers are non ionic polyoxyethythlene polyoxypropylene copolymers used in pharmaceutical formulations as emulsifying or solubilizing agents. They are used as emulsifying agents in intravenous fat emulsions.[20]Solid dispersions were prepared by fusion or melting method. Drug and Poloxamer 188 are in ratio 1:1 to 1:10.

iv. Tween80

Polysorbate 80 is non ionic surfactant. It is derived from polyethoxylated sorbitan and oleic acid. The hydrophillic groups in compound is polyether (polyoxyethylene group) which is polymer of ethylene oxide. Numeric designation following polysorbate refer to lipophilic group. Solid dispersions were prepared by fusion or melting method. Drug and Polysorbate 80 are in ratio 1:1 to 1:5.

III. BCS Class III Drug

Drugs which have high solubility but low permeability. For drug, permeability is the rate limiting step for drug absorption. For increasing permeability, permeability enhancement method are taken into consideration. Polymer generally enhance the permeability by drug vehicle based. Following are some commonly used agent being used in formulating BCS III drug.

i. Tween80

Polysorbate 80 is nonionic surfactant. It is derived from polyethoxylated sorbitan and oleic acid. The hydrophillic groups in compound are polyether(polyoxyethylene group) which polymer of ethylene oxide. Tween 80 is used both for solubility and permeability enhancement.

ii. Sodium Lauryl Sulphate

SLS is an anionic surfactant. It is prepared by ethoxylation of dodecyl alcohol, which is being produced industrially from palm kernel oil or coconut oil. The end product ethoxylate is converted to a half ester of sulfuric acid, which is neutralized by conversion to the sodium salt. These are added in formulations to increase permeability.

iii. Span40

SPAN 40 is a polysorbate which is derived from the mixture of partial esters of sorbitol treated with palmitic acid. SMP is a lipophilic surfactant. It may be found in combination with polysorbates. It is used to modify crystallisation of fats**.** These polyer are added to increase permeability of BCS III drug.

IV. BCS Class IV Drug:

Drug belong to this class have low solubility and low permeability. The solubility and permeability are rate-limiting step in manufacturing formulation of BCS IV drug. Generally, these drug are not used for formulation of oral fast dissolving film as it is difficult to increase both solubility and permeability of particular drug.

Manufacturing Method:

Solvent casting method: Most commonly used.

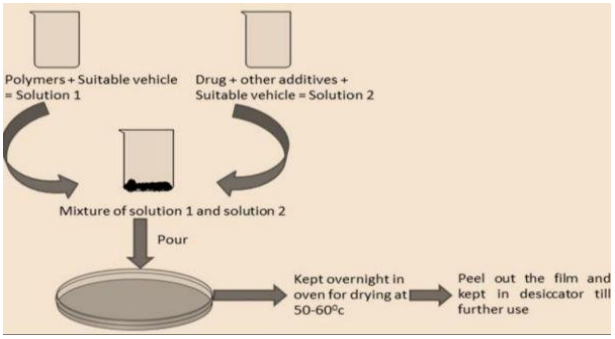

Figure: 1 Procedure of Solvent Casting Method

Semisolid Casting Method

- The ratio of acid insoluble polymer and film forming polymer should be1:4.
- Solution of water soluble film forming polymer is prepared. Formed solution is added to a solution to solution of acid insoluble polymer. Appropriate amount of plasticizer is added to that gel mass is obtained. Then, gel is casted in to film or ribbon casting using heat controlled drums.

Hot Melt Extrusion Method

Used to form granules or pellets, sustained release tablets, transmucosal and transdermal drug delivery system.

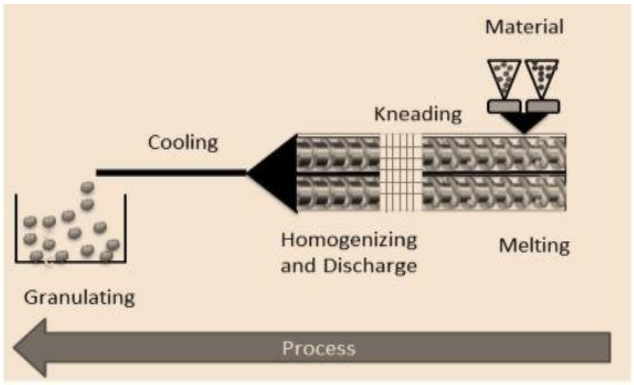

Figure: 1 Procedure of Hot melts extrusion method

1. **Solid Dispersion Extrusion Method:**

- Dispersion of one or more active materials in an inert carrier in a solid state in presence of amorphous
- hydrophilic polymer is said to be solid dispersion.
- Drug is dissolved in a liquid solvent. The solution is incorporated in to melt of Polyethylene Glycol obtained
- below 70°C.The solid dispersion are shaped in to the film by means of dies.

2. **Rolling Method:**

The solvent is water or mixture of water and alcohol. Prepare premix with film forming polymer, polar solvent and other additive. Add premix to master batch feed tank. Fed it via a first metering pumps and control valve to either or both of 1st and 2nd mixer. Blend the drug with master batch premix to give a uniform matrix. Specific amount of uniform matrix is then fed to the pan through 2nd metering pumps. The film is finally forced on the substrate and carried away via the support roller.The wet film is then dried using controlled bottom drying

Packing and Storage of Fast Dissolving Film:

Blister card can be used as a packaging system for films. Single/unit packaging system is required. Widely used packaging- aluminum pouch, stored in a dry place.[21]

EVALUATION OF FAST DISSOLVING FILM:

The film produced by anyone of the above manufacturing method, then, they are subjected to evaluation. Evaluation is a step to maintain inter- and intra-batch uniformity between films. Various evaluation parameters are as follows:

Organoleptic Evaluation - prepared films are analyzed for itsproperties.[22]

Morphology study - the scanning electron microscopic at fixed magnification is used to check morphology of prepared film.[23]

Thickness - the film thickness is measured by micrometer orscrewgauge.[24,25]

Weight variation test - the average weights are determined by weighing each film, and then, the average weight of the films is subtracted from the individual filmweight.[26]

Texture and physical appearance -texture is checked by simple touch and appearance to be determined simply with visual infection offilms.[27]

Folding endurance - the film again and again folded at same pointuntil get breaks. Folding endurance value is considered as number of times, it is folded withoutbreaking.[27]

Tensile strength (TS) - it is calculated by[28]

TS=Load applied at failure × 100 /film thickness × width of film.

Drug content uniformity - the assay method described in pharmacopeia is followed. It is determined by measuring the drug content in the individualfilm.[28]

Surface pH- the prepared formulation is taken to glass plate for 30 s containing water. The pH is noted after bringing the electrode of the pH meter in contact with surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was done.[29]

Moisture content- The amount of moisture present in the preparation affect the brittleness and friability of the films. The amount of moisture present in prepared film can be determined using Karl Fischer titration method/weighing method, a specific size of weighed film is heated at 100-120°C until it attains constant weight and the difference in weight gives the amount of moisture present in the film. Moisture content can be calculated by following formula:

% Moisture content = [(Initial weight - Final weight)×100/initial weight] [30]

Disintegration time - Disintegration time of film carried out using U.S.P. disintegration apparatus. The disintegration time should be about 30s or less for mouth dissolving strips. Disintegration time will vary depending on the formulation ingredients but typically the disintegration range from 5 to 30 s. Although there is no official guidance available for mouth disintegrating films.[30]

In vitro drug release - it is carried out by USP XXIII Type II apparatus in phosphate buffer pH 6.8 in 500 ml media and 0.1N HCl 500 ml media at the temperature is 37±0.5°C, and the rotation speed should be 50 rpm. The samples are withdrawn at various time intervals and should analyzespectrophotometrically.[30]

Percentage elongation - it is the percentage ratio of the rise in length to the original length [46]. Youngs modulus(YM)-[31]

YM = (Force at corresponding strain/cross section area)×1/(corresponding strain)

Stability studies - it is to be conducted as per the International Conference on Harmonizationguidelines.[31]

Various Technology used in Oral Film Formulation:[1]

XGel: XGel film technology can be taste masked, coloured and layered, whilst also having the ability to incorporate active pharmaceutical ingredients. It can be made encapsulate any oral dosage form and can be soluble in either cold or hot water. It was developed by Bio Progress Technology International, UK based had, sold the first powder fill version of its, XGel Film System.

Sol leaves: This is applied to flavour release product such as mouth freshners, confectionary and vitamin products. SOLULEAVES technology can be used to deliver active ingredient to oral cavity efficiently and in a pleasant and easily portable form.

Wafer tab: WAFERTAB is a advance form of fast oral delivery system that uses a unique process to prepare drugloadedthinfilmwhichcanbeusedinoralapplication.Active Ingredientisincorporatedaftercasting.

Foam burst: FOAMBURST is a drug delivery system in which is for capsule made foamed film. Gas is blown into the film during production, result in film of honeycombed structure. The void present in film may be gas filled, empty or filled with other material and produce specific taste characteristics or to deliver active drug. The light honeycombed structure of capsules that dissolve rapidly, causing a melt-in-the mouth sensation.

Micap: Micap combine with Bio Progress in micro encapsulation technology for formulation of water-soluble films. The developments will be aimed at providing new delivery mechanisms for the $1.4bn global market for smoking cessation products (SCPs).

Pharmaceutical Application of Oral Film:[9]

- **AllergicReaction-** Fastdissolvingfilmareusedtotreatallergicreactionduetobetterandfasterresponse.
- **CNS Disorder-** The oral film are beneficial to CNS disorder due to better response.
- **Topical Application-** The film are used topically as analgesic or antimicrobial agent for treatment of wound and cure.
- **Gastro retentive Dosage Form-** These are used to treat GIT disorder.
- **Vaccine-** The fast dissolving film can be delivered in form of vaccine to treat various diseases. Ex Rotavirus Vaccine.

Table: 2 List of Oral Film available in Market[16]

S. No	Oral Film	Active Ingredient	Category
1.	Klonopin Wafers	Clonazepam	Antianxiety
2.	Chloraseptic	Menthol/Benzocaine	Sore throat
3.	Gas-X	Simethicone	Antiflatuating
4.	Triaminic	Diphenyhydramine HCl	Anti allergic
5.	Supress R	Menthol	Cough Suppressant

CONCLUSION

The present review concluded that due to dysphagia problem and emergency patient, Fast oral dissolving film are generally used. It increase patient compliance and easy to administer. Drug belongs to BCS II and BCS III, rate limiting step of absorption create difficult in manufacturing even drug which have low dose. It can be corrected with help of polymer. Among all the manufacturing method, solvent casting method is commonly used. Wafer, Foamburst, Micap are some technique which are used to oral film formulation.

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