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A Review on Formulation of Oral Dissolving Film

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ABSTRACT

Oral dissolving films are known for its rapid action. The oral route is the common route for conveying the drug. The tablets and capsules are the widely used medicaments in oral dosage form. But now for most of the paediatric, geriatric and dysphagia patients who finds difficulty in swallowing, the Oral Dissolving Films (ODF) can be given to overcome such problems. The formulation of Oral Dissolving Films does involve polymers, plasticizers, surfactants, flavours and sweeting agents. This review aims to give an overview about the preparation, formulation techniques and the recent technologies used in the ODF formulations. The solvent casting method is the widely used technique in the preparation of thin films.

Keywords: Oral dissolving films; Preparation techniques; Methods; Technologies

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INTRODUCTION

A novel oral delivery system, oral dissolving films were prepared based on transdermal patch technology. A thin oral strip is prepared and is placed on the patient's mucosal cavity where it is wetted by saliva making it adhere to the surface. Polymeric films have shown great potential in delivering medications into oral cavity. It's preferred by patients who have medical conditions that make it difficult for them to swallow or chew other solid oral dosage form [1]. Some advantages of oral dissolving films are

There is no water needed
Convenient and accurate dosing
Less possibility of chocking

Though there are some drawbacks such as

Oral dissolving films are moisture sensitive
High dose cannot be given in oral film
Easily breakable.

Oral dissolving films are mainly preferred for paralysis, mental disorder and dysphagia patients as they cannot swallow large quantities of water. Common drugs which are available in the form of films are antiulcer, anti-asthmatics, antitussives, expectorants, antihistamines and Non-Steroidal Anti-Inflammatory Drugs. Oral dissolving films are classified as,

Table 1: Types of films and their properties

Property/subtype	Mucoadhesive sustained release	Mucoadhesive melting film	Flash release
Structure	Multilayer	Single/multilayer	Single layer
Area(cm^2)	02-Apr	02-Jul	02-Aug
Thickness	50-250	50-500	20-70
Drug phase	Solid solution/Suspension	Suspended drug particles or solid solution	Solid solution
Excipients	Non-soluble/low polymers	Hydrophilic, soluble polymer	Highly hydrophilic soluble polymers

EXPERIMENTAL SECTION

Materials used in Preparation of Film

Polymers

The selection of polymers plays an important role in the successful formulation of Oral Dissolving Films, for the preparation of ODF they can be either used alone or in combination with other polymers. The rectitude of the ODF's depends on the concentration and nature of the polymers, generally 45% is the optimal concentration of the polymer for the preparation of ODF. The commonly used polymers are HPMC K5, CMC, PVP K90, pectin, sodium alginate, HPC. HPMC is proved to be a better polymer than others [2].

Ideal Properties of Film Forming Polymers

The polymers should be inert, nontoxic and non-irritant.
The polymer should have a better mouth feel property and good shelf-life.
The polymer should exhibit good spread ability and wetting property.
The polymers need to possess sufficient tensile, shear and peel strengths.
The polymer should be economical and readily available.

Plasticizers

The properties like tensile strength and elongation are directly related to the concentration of the plasticizers, the plasticizer concentration for the preparation of ODF ranges from 0-20% w/w. Plasticizers that are commonly used are glycerol, polyethylene glycol, triethyl citrate [3].

Surfactant

Surfactants often play an important role in dispersing, wetting and solubilizing thus helping disintegration of the films. The most commonly used surfactants are tween, SLS, benzalkonium chloride, polaxamer [4].

Flavour

Flavours are the agents that are added to mask the unpleasant taste of the drug; the concentration of flavour depends upon its strength and nature. The FDA approved flavours can be used for the formulation, the commonly used flavouring agents are liquorice, mint and sucralose [5].

Sweetening Agents

Sweetening agents are the substances that are designed to disintegrate or dissolve in the oral cavity. Neotame and Alitame are 2000–8000 times sweeter than sucrose. Fructose has more sweetening power compared to sorbitol and mannitol. Sucralose was found to be 600–1000 times sweeter than sucrose when Oral Dissolving Films of a drug was evaluated for taste, after taste mouth feel. Aspartame and saccharin sodium are likely to be 200 and 300–500 times sweeter compared to sucrose, respectively. It was also reported that sweeteners and flavours have minor effect on flexibility of film, but the natural sweeteners are chosen over artificial sweeteners due to the safety of the natural sweeteners, some of the water soluble natural sweetener are ribose, glucose, xylose, maltose etc [6,7].

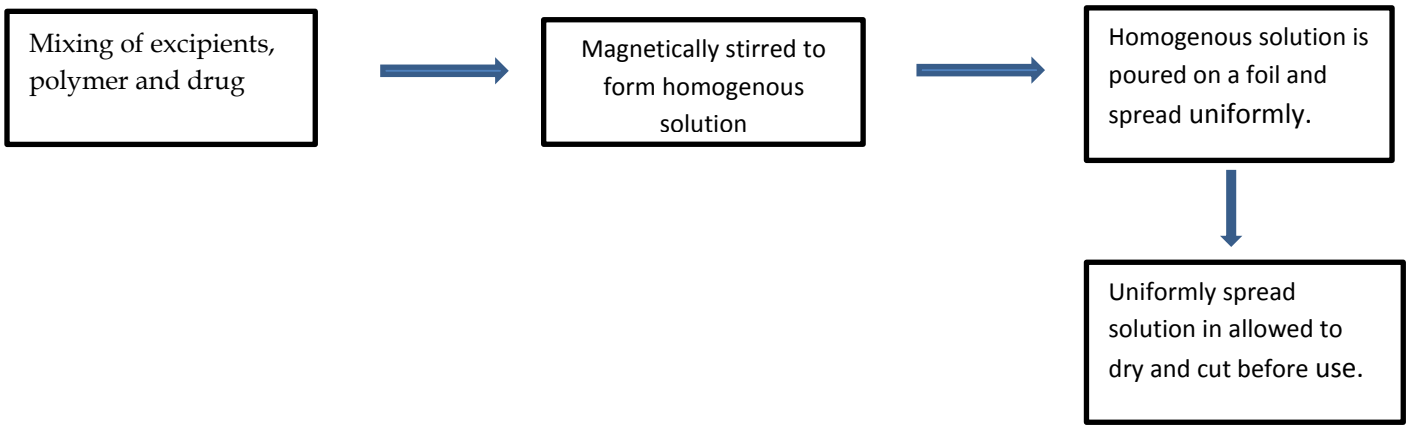
Methods of Preparation of Films

There are some methods in which oral dissolving films can be prepared, each of the methods are described below

1. Preparation of film using, Solvent casting method
2. Semisolid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling method

Solvent Casting Method

It is one of the commonly used methods for the formulation of film. It is prepared using water soluble polymers, excipients and drug. Due to the application of high shear force a homogenous mixture is formed (Figure 1). The solution obtained is poured into foil spread with coating knife to obtain uniform thickness [8].



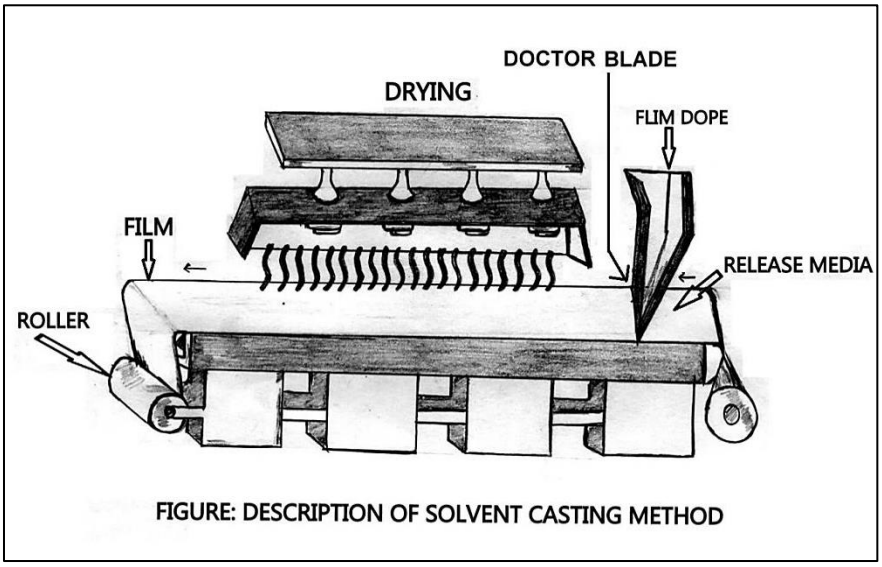
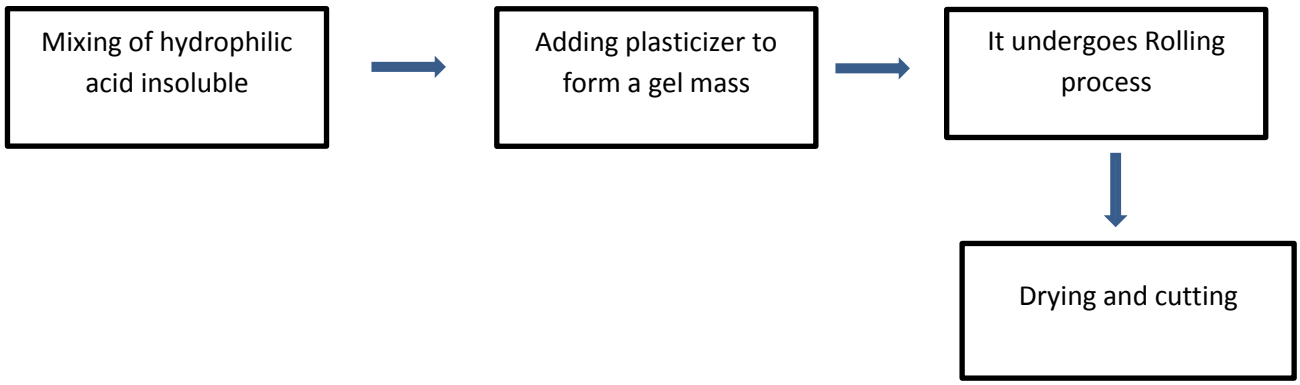


Figure 1: Solvent casting method

Semi Solid Casting Method

In this method water soluble polymeric film is prepared then the polymeric solution is added to acid insoluble polymeric solution .The sufficient quantity of plasticizers is added to obtain gel, the gel is casted into plate by required thickness. The acid insoluble polymer and water soluble polymeric solution should be in the ratio1:4 [9-12].



Hot Melt Extrusion

It is a process in which polymer undergoes melting due to applied heat and pressure. It is mostly used in the preparation of SR-tablets, granules.

This method breaks the ancestral way used for preparation of ODF. In this film is prepared through heating process. Ingredients are mixed in a dry state after the process of heating it's taken out in a molten state. Molten mass obtained is used to cast film. Then films are cooled and cut. Major drawback of this technique is the Active Ingredients is deactivated due to the high temperature. Vital step in this technique is casting and drying (Figure 2). Correlated to HME technique solvent casting occurred to be more up righted process for production of ODF [9, 11].

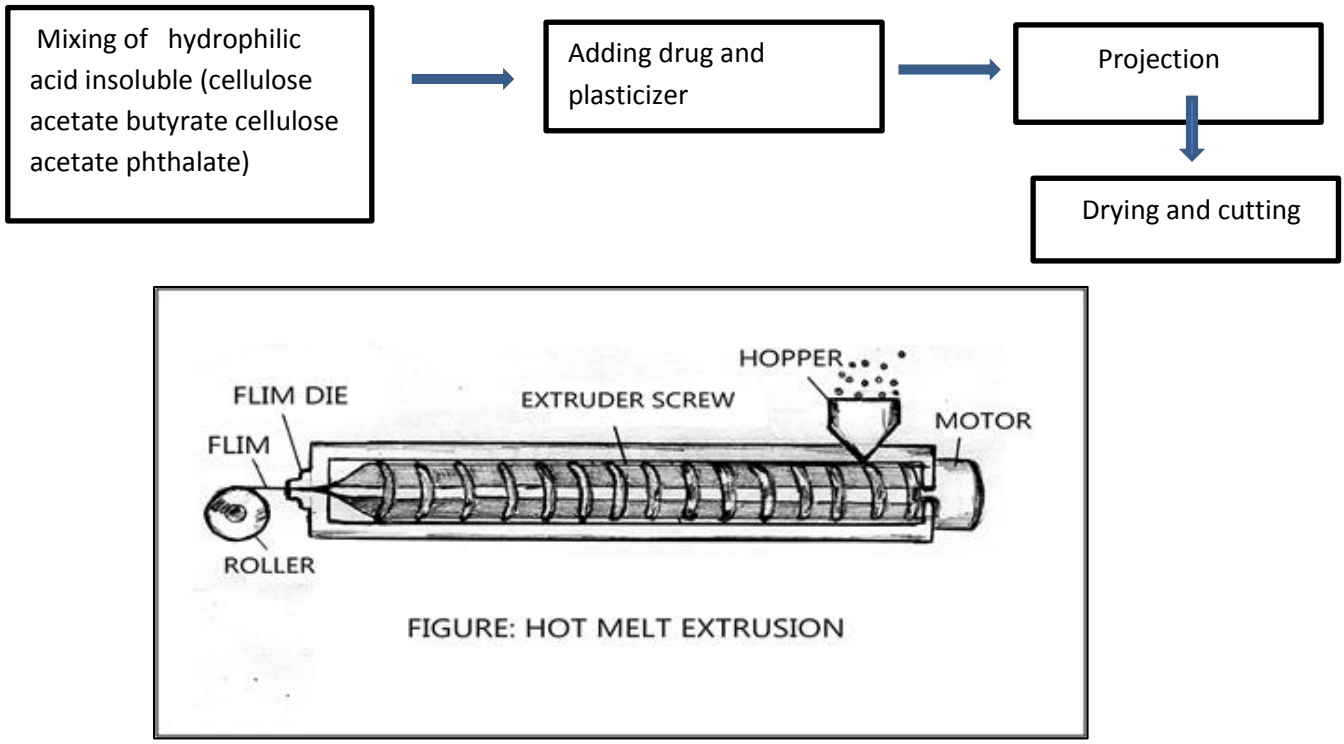
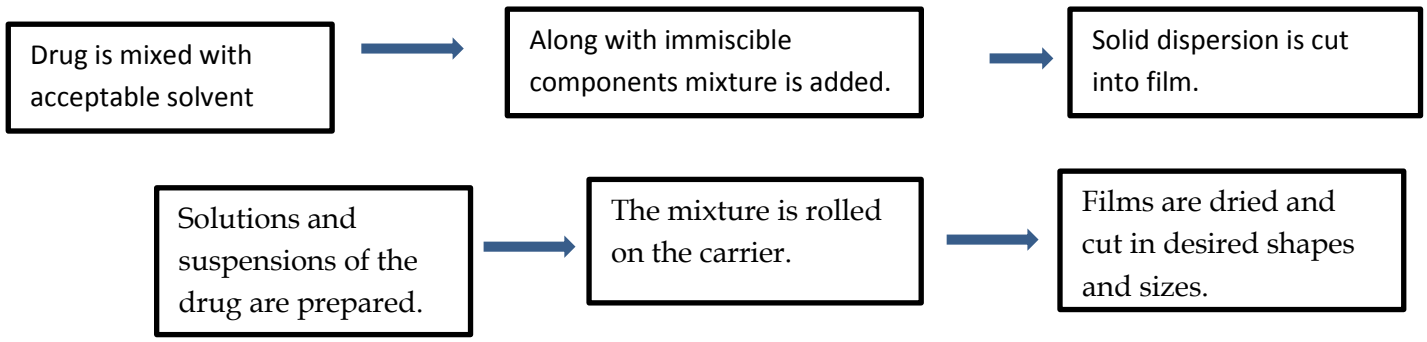


Figure 2: Hot melt extrusion technique

Solid dispersion method:

In technique drug this is dissolved in pitiable solvents and solution is merged into melted PEG under 70°C. Solid dispersion are at last carved to films by use of dies [12,13]. In this method either suspension or solution containing API is placed on the carrier and rolled. Mainly combo of alcohol and water or only water acts as a solvent (Figure 3). ODF on rollers is dried and cut into desired size and shape [14,15].



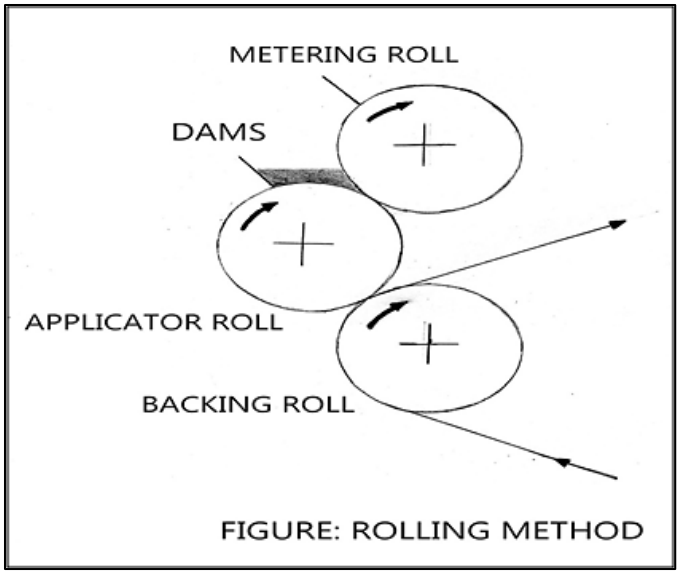


Figure 3: Rolling method

Recent Manufacturing Technologies

XGel:

This type of film is mostly preferred by vegetarians as the film is not made from sources of animals. It is used to mask the taste, the colour, the layer and they have enteric properties .it also include API. As they are water soluble, it can be used for developing any kind of oral dosage form [10]. It can be prepared in various shapes and sizes. It is an excellent method for delivering the medicines.

Soluleaves:

The soluleaves are added for those agents that release flavours such as confectionaries, fresheners and vitamin. It is used to deliver the pharmaceutical active ingredient to the oral cavity in efficient and pleasant way; this technology is used for wide range of products for ODFs. The soluleaves are made to dissolve quickly when the film comes in contact with the saliva, which release the API quickly. Due to this reason soluleaves are excellent for wide range release by oral administration. This technology is often suited for paediatric, geriatric patients who have difficulty in swallowing tablet and capsules [10].

Wafertab:

Wafer tab is one of the different processes to load a drug in then films for topical or oral administration. After casting into the films API ingredients are added to it. In this system in which drug is in the form of ingestible filmstrip, this technology gives quick dissolution and release of the drug when it comes in contact with saliva. Wafertab is also used for making and improving the taste. The drug is accruable weighed included in the pre manufactured film to prevent moisture and heat and helps in increasing the stability of the product .Wafertab helps to achieve more possibilities in innovation of drug. Wafertab are formulated in various shapes and sizes and it helps in quick release of drugs and also the patients who can't swallow easily [10].

Foamburst:

Their new potent was accepted in 2004 on the month of September. In which using foamed film capsules are prepared. Foamburst is an alternative of Soluleaves. Honeycombed structure is formed due to the gas blown into the film during the manufacturing process gases filled in the free space of the film. It causes melt in mouth sensation due to the honeycombed structure which is formed lightly as a result capsule dissolves quickly [10].

Micap:

In the year 2004 Micap signed a bond which was a choice to merge its facility in micro encapsulation process with Bio progress water soluble film. They are Bioscience Company using a single cell organism they develop patented micro-encapsulation processing single cell organism they produce a natural micro capsules for Agro chemical, food and pharmaceutical industries [10].

Evaluation of fast dissolving oral films

General appearance

ODFs are either transparent or semi-transparent.

Film weight

The weight of the Oral Dissolving Films is determined by analytical balance ODF's are expected to have a constant weight with desirable amount of pharmaceutics ingredients and excipients.

Evaluation of organoleptic evaluation:

The colour is the one of the important criteria as its acts as an identification of pharmaceutical product [16,17]. The colour should be uniform and it should have consumer acceptance

Odour: Odour is an important factor to be evaluated for the ODF's. The odour in the dosage from often indicates the odour of the API or the excipient and also sometimes it indicates the stability of formulation [17].

Taste: Taste of the formulation is directly related to the consumer acceptance now a days many In-vitro methods are being utilizing the taste sensors which are designed for the taste testing purpose [16,17].

Thickness:

The calibrated vernier calipers/ micrometre screw gauge used to evaluate the thickness of the film. The film thickness is measured at five different including four corner and centre. Thickness in the film has direct relation with accuracy of dose [18].

Mechanical Properties

Tensile strength:

It is defined as the point at which the film breaks due to the application of maximum stress. This test is carried to determine the mechanical strength of the ODF [18]. The tensile strength can be calculated by the equation [19,20, 21].

$$\text{Tensile strength} = (\text{failure load}/\text{strip thickness} \times \text{width of strip}) \times 100$$

Folding endurance:

In the folding endurance test the folding of the strip is carried out until the strip breaks at a same point. The folding endurance is the measure of total number of folding of the film without breaking [20,21].

Young's modulus:

It was first carried out by Giordane riccati it is also called as the elastic modulus; it is the measure of rigidness of the film and is defined as the ratio of stress applied to cause elastic deformation of the film [21].

$$\text{Young's modulus} = \text{Slope} \times 100 / \text{thickness of film} \times \text{Crosshead speed}$$

Tear resistance:

It is defined as the maximum force which is required to tear the film. The rate of loading recruit is 2 in/min. which is planned to determine the magnitude of force required to initiate tearing in the film specimen [22].

Percentage elongation

The film elongates as the concentration of the plasticizer increases, the film extends or stretches when the force is applied, it is called strain. The strain is the bending of the film to the original sample dimensions [22].

Disintegration time

The disintegration time of oral dissolving film ranges from 5 to 30 seconds. Mostly Though there is no official method available for determining disintegrating of oral dissolving films. Two methods are carried out for determining the disintegration time of the film as follows [22].

Slide frame:

In this method the film is clamped into slide frame after dropping a drop of water on the film.

Petri plate method:
Here in this method the film is placed on the petridish and 2ml of distilled water is added to it, the amount of time taken by film to dissolve completely is called as the disintegration time.

Table 2: Some recent fast dissolving oral film formulation attempts and their advantages

Preparation	Advantage	Authors
FDOFs of amlodipine besylate were developed	Rapid disintegration dissolution, better patient compliance and better tensile strength	Shelke et al.,2012 [24]
FDOFs containing dexamethasone as an antiemetic medication were developed	Rapid disintegration, better patient compliance and better tensile strength	Minako et al.,2012 [25]
FDOFs of citalopram hydrobromide were developed	Good dissolution profile and tensile strength	Rubia et al.,2012 [26]
FDOFs of domperidone were developed	Better dissolution profiles and tensile strength.	Joshi et al.,2012 [27]
An innovative Rapid film have been developed for ondansetron	Rapid film and conventional oral dispersible dosage both were found bioequivalent	Reiner et al.,2010 [28]
Oral film and microbicide gels have been studied	Novel technique has been developed for vaginal delivery to prevent HIV transmission.	Garg et al.,2010 [29]
Dexamethasone and pilocarpine were used as API and Pullulan was used as polymer in FDOF	Results showed that Pullulan in 2% concentration gave better drug release	Murata et al.,2010 [30]
Rapid film of cetirizine dihydrochloride using Pullulan as film forming agent has been developed	Good patient compliance, strength and masking taste	Mishra et al.,2010 [31]
Comparison of different polymers in formulation of oral films	Pullan and HPMCE-15 were found to be best film formers among all selected polymers	Kulkarni et al.,2010 [32]
Authors have studied the effects of taste masking agent and nicotine on properties of nicotine film was studied	Different flavours were used for taste masking and milk flavour gave better taste masking effect	Francesco Cilurzo et al., 2010[33]
Fast dissolving films made up of Maltodextrins have been studied	Better patient compliance, strength, and Good flexibility	Francesci Cilurzo et al.,2008 [34]
FDOF using Pullulan have been prepared and variable concentrations of Pullulan have been used	Increased in disintegration and better dissolution profiles	Saini et al., 2011 [35]
Ondansetron FDOF was compared with oral disperasable tablet for vomiting	Higher patient convenience	Valentina et al.,2010 [36]
Dexamethasone FDOF for cancer induced vomiting and radiotherapy patients	Rapid disintegration better patient compliance and rapid drug release	Shimoda etal., 2009 [37]

***In-vitro* dissolution test:**
Commonly USP Ⅰ (basket) and USP Ⅱ (paddle) are to carry out the test. In the in vitro dissolution process sink condition should be maintained sometime during the test ODF's floats on the medium .So there is difficulty in performing the test in proper way. This issue is mostly faced by the USP Ⅱ apparatus. The phosphate buffer 300ml of PH6.8 and 900 ml of 0.1N Hydrochloride is used as media Temperature maintained at 37 ± 0.5℃. Generally 50 rpm of rotation speed is maintained samples are taken at the intervals and analysed in Ultra Violet Spectrophotometer. Despite its expansive use dissolution test is still prone noteworthy inaccuracy and tests let down [38]. Recently they have carried out new bio-relevant *in vitro* dissolution test for oral dispersible film.

One chamber method:
In this method set up is based on USP Ⅱ in this method different sample application used. in the first way the film is put to dissolution medium and in secondary the film is to be kept in a cylindrical shaped sinker containing a mean size of 0.36to 0.44m. This is done to avoid the floating of the films. In the third way the film is attached to glass, because of the improper film adhesiveness, No bilayer adherence tape is required [23].

Punch and Filter method:
This method is based on the setup of paddle apparatus this device contains filter paper and it is to be cut into a required dimension to create flat interface between the stainless frame and the filter. ODF's are held at a top of filler after adjusting the ODF and the punch. The ODF"s were kept in the dissolution media from bottom to top side to identify the status of dissolution, in this process active pharmaceutical ingredient diffuses inside the filter located in the second chamber, this method is used to calculate the stimulated saliva flow and it helps in masking the taste of new ODF"s or to improve the absorption of the films.

CONCLUSION

The oral dissolving films are considered as the novel work in the pharmaceutical field, this approach of delivery system is best suited for geriatric, paediatric and psychiatric patients who have difficulty in swallowing, so this approach exhibits less risk and improved patient compliance with higher safety. Since ODF's bypasses the hepatic metabolism, its ease of administration and requires no water at the time of drug administration makes this delivery a unique one, and improves the therapeutic response significantly. The Recent Manufacturing Technologies like x-gel, waferbust, soluleaves and foam burst helps in increasing the compliance by masking the taste, odour and colour of the formulations.

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