ejpmr, 2024, 11(3), 55-63

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

ORODISPERSIBLE FILMS - A REVIEW

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Article Received on 01/01/2024 **Article Revised on 22/01/2024** **Article Accepted on 12/02/2024**

ABSTRACT

Oral application is the most acceptable, non-invasive, and widely used route of drug administration. Various dosage forms for oral drug delivery: syrups, suspensions, drops, tablets, capsules or chewing gums are available. However, each of them raises some problems related to their administration and dosing. Moreover, several groups of patients have considerable swallowing difficulties, dysphagia, or fear of choking, which hamper their therapy as well as complicate patient compliance and adherence. To eliminate difficulties exhibited by traditional solid oral dosage forms and meet the expectations of today's patients, more and more formulations appear as orodispersible drug delivery systems, orodispersible films (ODFs). Orodispersible films (ODFs) are novel drug delivery systems for the oral delivery of the drugs in an ultra-thin film form prepared using hydrophilic polymers that rapidly dissolves on the top or the floor of the tongue or buccal cavity. Use of orodispersible formulations avoids the risk of choking, which may occur in the case of conventional tablets or capsules. It is also suitable for patients who are not willing to cooperate or face the difficulties associated with complete dosage intake, such as patients with depression, schizophrenia, dementia, and other neurodegenerative diseases. ODFs are at the cutting edge of drug technology as they offer a good alternative for rapid drug delivery.

KEYWORDS: Orodispersible films, formulation, mechanical properties, packaging.

INTRODUCTION

Pharmaceutical and clinical research industries are moving towards new paradigm of personalized medicines. This opens a new window of opportunities for small scale extemporaneous formulations in the pharmacy settings. There is an increasing need of developing new drug delivery platforms to address the needs of special patient populations. Orodispersible films (ODFs) are well-suited to address the needs of special populations such as pediatric, geriatric and patients suffering from dysphagia, nausea/vomiting or on restricted fluid intake. Even many pediatric and geriatric patients are unwilling to take solid preparations due to fear of choking due to its tablet type appearance. These patient groups often require specially compounded preparations as they are unable to swallow traditional solid dosage forms.[1]

Orodispersible films are novel drug delivery systems for the oral delivery of the drugs in an ultra-thin film form prepared using hydrophilic polymers that rapidly dissolves on the top or the floor of the tongue or buccal cavity. It is an ultra-thin strip (10-100 microns thick) of postage stamp size with an active agent and other excipients which will disintegrate within 30 seconds. The ODFs can be prepared by solvent casting, evaporation, hot melt extrusion, or electrospinning methods. The excipients used are film-forming water-soluble polymers, plasticizers, sweeteners, surfactants, and saliva stimulators.[2,3] Oral films are not suitable for treatments requiring high doses (i.e., >100–150 mg), Dose can be modulated by modifying the size, solubility, and the thickness of the film.[4]

Salient Features[5]

- Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Rapid dissolution and absorption of the drug, which will produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased.
- Pre-gastric absorption can result in improved bioavailability and because of reduced dosage;

improve clinical performance through a reduction of unwanted effects.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra-rapid on set of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

Table 1: ODFs available on the market as OTC and prescription drugs.

Brand name	API	Use	Category
Chlorseptic sore throat strips	Benzocaine	Sore throat relief	OTC
Gas X thin strips	Simethicone	Reducing bloating	OTC
Risperidone Hexal	Risperidone	Schizophrenia	Rx
Sudafed PE	Phenylephrine HCl	Relief of stuffy nose	OTC
Zuplenz	Ondansetron	Nausea and vomiting	Rx
NiQuitin	Nicotine	Nicotine withdrawal symptoms	Rx

Advantages of Orodispersible Films[6,7]
- ODFs have a pleasant taste, are easily soluble after contacting saliva, are easily ionized when they disintegrate on the tongue and penetrate the mucosal membrane and provide prompt drug action.
- They are stable, efficacious, have improved absorption and higher bioavailability.
- They have higher patient compliance because geriatric, pediatric, and paralyzed patients can easily take them without water and without choking problems.
- ODF technology helps to incorporate drugs at low doses as well as drugs that are incompatible with the gastrointestinal tract and bioavailability problems are easily resolved.
- The development process of ODFs is easy and can be completed within a few days.
- They provide quick effects in emergency conditions such as asthmatic attack, migraine attack, angina attack, and in intraoral diseases.

Limitations of Orodispersible Films
- Require special equipment for packaging and storage.
- This technology is not suitable for drugs with large doses.
- They are hygroscopic and therefore susceptible to deterioration, which makes them difficult to protect.
- They have fast dissolution and disintegration processes, so dose termination cannot be like that of tablets.

CLASSIFICATION OF ORODISPERSIBLE FILMS[6]

ODFs are generally classified into three classes: type 1, according to dissolution; type 2, according to layering; and type 3, according to the nature of the API.

Type 1 ODFs: Type 1 ODFs are divided into three subclasses: fast, moderate, and slow. Films that dissolve within thirty seconds are termed fast-dissolving ODFs and have a thickness of around 50–150 µm; films that dissolve within one to thirty minutes are known as moderately dissolving ODFs; and slow-dissolving ODFs can take more than thirty minutes to dissolve. Fast-dissolving films are used in emergency conditions, while slow/moderately dissolving films are used to prepare nicotine-based products, as they help to lessen or eradicate cravings in patients who have used tobacco regularly and become dependent.

Type 2 ODFs: Type 2 ODFs are classified according to the number of layers they contain. Layers can be monolayers, bilayers, or multilayers. Monolayer oral films consist of an API, a film-forming polymer, and excipients, while bilayer or double layer films consist of one API layer and another taste-masking or permeation-enhancing layer. In multilayer films, the API layer is sandwiched between two layers.

Type 3 ODFs: Type 3 ODFs are further classified according to API source, which may be synthetic, e.g., sildenafil, or natural (animal or plant), e.g., ginger and turmeric. Films prepared using minerals, vaccines, vitamins, or micronutrients constitute the other class of type 3 ODFs, e.g., vitamin D ODFs. All these ODFs contain prescription drugs or over the-counter drugs, while ODFs prepared from plant sources are difficult to fabricate.

FORMULATION CONSIDERATION[6,8,9,10]
- Active pharmaceutical ingredient
- Film forming polymers
- Plasticizer
- Sweetening agent

- Saliva stimulating agent
- Flavouring agent
- Colouring agent

Active pharmaceutical ingredient (API)

The most important quality of a drug candidate for use in an ODF is that it belongs to BCS class 1, having high permeability and solubility, as well as a low MW with administrability at a low dose. Nowadays, however, companies and researchers are trying to prepare ODFs with drugs that belong to BCS classes 2 and 3. Researchers are also trying to prepare drugs with better tastes or with the masking of unpleasant tastes for better patient compliance. A list of drug candidates having low doses and low molecular sizes are presented in Table 3. The projected drug doses for ODF preparation generally range from 0.3 to 100 mg. Other than pharmaceutical ingredients films, ODFs have also been prepared using plant leaf extracts that have therapeutic activities, e.g., cannabinoids. Many APIs, which are potential candidates for ODF technology, have bitter taste. This makes the formulation unpalatable especially for pediatric preparations. Thus, before incorporating the API in the ODF, the taste needs to be masked. Various methods can be used to improve the palatability of the formulation. Among the techniques employed, the simplest method involves the mixing and co-processing of bitter tasting API with excipients with pleasurable taste. This is often termed as obscuration technique.

Table 2: Potential drugs for formulation in ODFs, along with their doses.

Drug	Drug class	BCS class	Dose(mg)	Category
Chlorpheniramine	Antihistamine	1	4-12	OTC
Loratadine	Antihistamine	2	5-10	OTC
Sildenafil	PDE inhibitor	1	25-100	Rx
Zolmitriptan	SSRA	3	2.5	Rx
Loperamide	Antidiarrheal	2	2	OTC
Nicotine	NCA	1	1-15	Rx
Valdecoxib	COX 2 inhibitor	2	5-20	Rx
Dextromethorphan	Antitussive	2	10-30	OTC
Ziprasidone	Antipsychotic	2	20-80	Rx
Nitroglycerin	Vasodilator	1	0.3-0.6	Rx

Film-forming polymers

Film-forming polymers are key components in the manufacturing of ODFs. To strike a balance between mechanical properties and disintegration time of ODFs, proper selection of polymer type and concentration is an important issue. Polymer properties are principally affected by their molecular mass. To compare the effect of molecular weight on film properties, ODFs were prepared with low and high molecular mass maltodextrin. Results of the experiment revealed that films made of maltodextrin with high molecular mass were stiffer and less sticky than those obtained with lower molecular mass maltodextrin. Moreover, their tensile strength and elastic modulus were higher, whereas elongation at break was lower. Viscosity of the mixture provided by the polymer prevents API sedimentation, provides homogeneous dispersion of all ingredients, and facilitates the manufacturing process. Ideal viscosity should be high enough to prevent sedimentation of particles, but at the same time not too high to avoid problems during the manufacture. The most used polymers are cellulose derivatives, polyvinyl alcohol, and pullulan. There are examples of films based on mixtures of different polymers such as: Hypromellose and methacrylic acid copolymers; polyvinyl alcohol or polyvinylpyrrolidone and croscarmellose sodium; high molecular mass povidones and synthetic copolymers of macrogol-polyvinyl alcohol; carboxymethylcellulose, Hypromellose and sodium alginate.

Plasticizer

Plasticizer is a vital ingredient of the fast-dissolving films. Plasticizer helps to improve the flexibility of the strip and reduces the brittleness of the films. It significantly improves the film forming properties by reducing the glass transition temperature of the polymer. The chemical structure and concentration of plasticizers play an important role in alleviating the glass transition temperature of the polymers. The selection of plasticizer will depend upon its compatibility with the polymer and the type of solvent employed in the casting of film. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer. Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients. Typically, the plasticizers are used in the concentration of 0–20 percent; w/w of dry polymer weight. However, inappropriate use of plasticizer may lead to film cracking, splitting, and peeling of the strip. It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug.

Sweetening Agents

Sweeteners have become the important part of the formulation intended to be disintegrated or dissolved in the oral cavity. Generally, sweeteners are used in the concentration of 3 to 6%w/w either alone or in

combination. Both natural sweeteners as well as artificial sweeteners are used in the formulation of these fast-dissolving films. Polyhydric alcohols such as sorbitol, mannitol, and isomalt can be used in combination as they additionally provide good mouth-feel and cooling sensation. However, it should be noted that the use of natural sugars in such preparations need to be restricted in people who are on diet or in the case of diabetic patients. Due to this reason, the artificial sweeteners have gained more popularity in food and pharmaceutical preparations. Saccharin, cyclamate, and aspartame are the first generation of the artificial sweeteners followed by acesulfame-K, sucralose, alitame and neotame which fall under the second-generation artificial sweeteners. Acesulfame-K and sucralose have more than 200- and 600-time sweetness. Neotame and alitame have more than 2000- and 8000-time sweetening power as compared to sucrose. Aspartame was used for the preparation of oral strips of valdecoxib. Sucralose and neotame was reported to be used in the suppression of the bitter taste of fast dissolving films of diclofenac and ondansetron respectively.

Saliva Stimulating Agent

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations. Generally, acids which are used in the preparation of food can be utilized as salivary stimulants. E.g. Citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid. These agents are used alone or in combination between 2 to 6%w/w of weight of the strip.

Flavouring Agents

Preferably up to 10%w/w Flavors are added in the ODF formulations The acceptance of the oral disintegrating or dissolving formulation by an individual is largely depends on the initial flavour quality which is observed in first few seconds after the product has been consumed and the after taste of the formulation which lasts for at least about 10 min. The selection of flavour is dependent on the type of drug to be incorporated in the formulation. It was observed that age plays a significant role in the taste fondness. The geriatric population like mint or orange flavors while younger generation like flavors like fruit punch, raspberry etc. Flavouring agents can be selected from synthetic flavour oils, oleo resins, extract derived from various parts of the plants like leaves, fruits, and flowers. Flavors can be used alone or in the combination. Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavour oils while vanilla, cocoa, coffee, chocolate, and citrus are fruity Flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence.

Colouring agents: FD & C approved colouring agents are used (not exceeding concentration levels of 1 percent; w/w) in the manufacturing of orally fast dissolving films. E.g. titanium dioxide.

ODF TECHNOLOGY

While ODFs as a product was evolving from breath fresheners to prescription products, the patented technological platforms to fabricate ODFs were also evolving in parallel.

Table 3: List of patented ODF technologies.

Sl. No.	Name of the company	Patent number	Technology name
1.	Aquestive Therapeutics	US7,357,891	PharmFilm
2.	Hexal Pharmaceuticals	WO2007009801 WO2007009800 WO2010115724	Melting Film
3.	Labtech Gmbh	WO2008040534 WO2009043588 WO2011124570	RapidFilm
4.	Bioenvelope	WO2009055923	Thinsol
5.	Intel Genx Technology Corp	US20110136815	VersaFilm
6.	Seoul Pharma Co Ltd	WO2013129889	SmartFilm

THE DIFFERENT TECHNIQUES FOR THE PREPARATION OF ODFS

Solvent-Casting Method[11]

It is the most common method used for the preparation of the films because it is feasible due to straightforward method and low cost. Most used solvents are water and ethanol. Film-forming water-soluble polymers are dissolved or dispersed in the solvent and then the active pharmaceutical ingredient (API), plasticizer, and other excipients are added to the polymer solution and allowed to mix fitly for overnight using magnetic stirrer. Then, the solution is cast on a casting apparatus or glass mould using coating knife which properly distributes the solution. Let it to dry overnight in an oven at 40°C–50°C. Then, peeled and cut into desired size and shape.

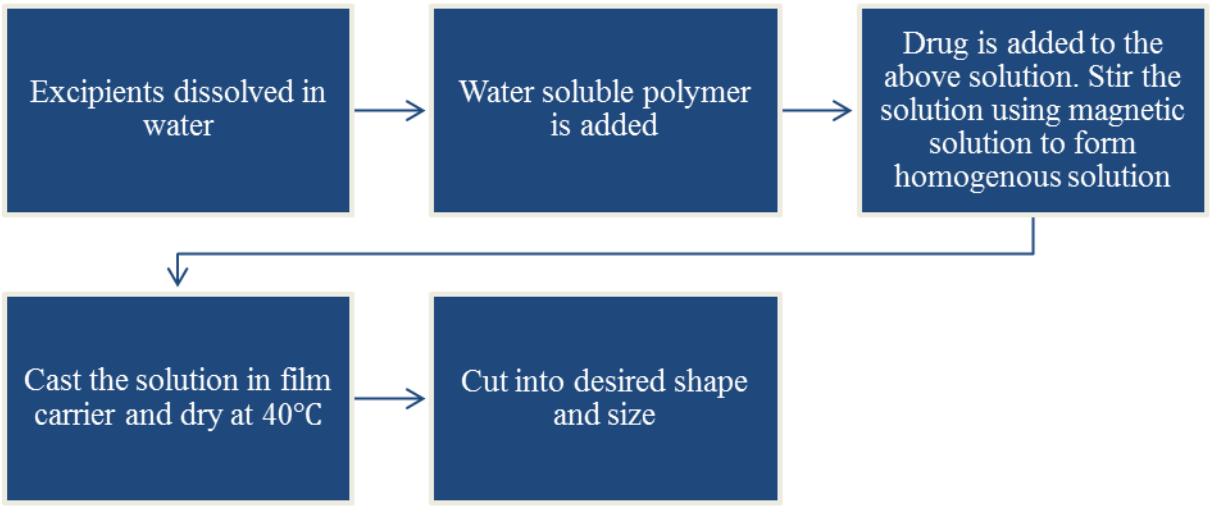

Figure 1: Flowchart for the process of solvent casting method.

Hot-Melt Extrusion[12]

It is substitute for solvent-casting method. It is used when there is no use of organic solvent. Hot-melting extrusion is a process of shaping the mixture of polymer, API, excipients into the film by melting all components. Then, the film is cut down into desired shape and size. This method is not suitable for thermolabile APIs because APIs are subjected at high temperature in this method.

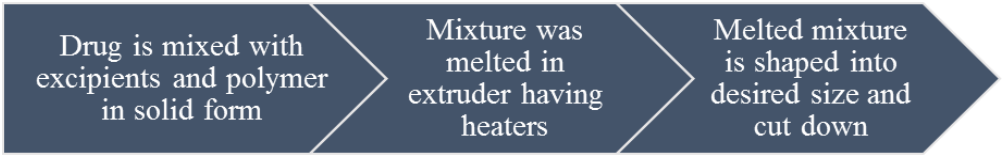

Figure 2: Process for hot-melt extrusion technique.

Semisolid casting[8]

This method is preferably adopted when acid insoluble polymers are to be used in the preparation of the films. In Semisolid casting method gel mass is casted in to the films or ribbons using heat-controlled drums. Gel mass is obtained by adding solution of film forming to a solution of acid insoluble polymer in ammonium or sodium hydroxide. Acid-insoluble polymers used to prepare films include: cellulose acetate phthalate, cellulose acetate butyrate. Acid insoluble polymer and film forming polymer should be used in the ratio of 1:4.

Spray Technique[11]

In this technique, the polymer is dissolved in the solvent and the API and other excipients are mixed in it to form a clear solution. Then, the solution is sprayed on a suitable material such as glass, polythene film of non-siliconized kraft paper or sheet that acts as carrier support. Let it dry and then the film layer is peeled off and cut into the required size and shape.

Electrospinning[13]

Electrospinning is another solvent-based technology explored to produce ODF characterized by a high-porous inner structure (Vasvári *et al.*, 2018). Although differences among electrospinning machineries, the basic set-up consists in a metallic needle, through which the formulation is pumped with a controlled flow and charged under a high-voltage electric current in the 10–35 kV 7 range, above an opposite-charged collector (Huang *et al.*, 2019). The active substance can be loaded both before and after the spinning process (Thakkar and Misra, 2017). In the former case, the main advantage is the improvement of the drug dissolution rate due to the huge surface area of nanofibers. In the latter case, placebo ODF can be embedded by the drug solution and dried, widening the possible applications of such technology.

Rolling Method[11]

In this method, the API, polymers, and other excipients are mixed with the suitable solvents, for example, water and alcohol. Then, the solution or suspension containing API is rolled on carrier. Then, the film is dried and cut into the desired shape and size.

3D Printing[14,15]

Over the past few years, researchers have also tried to develop ODFs using a new technique, namely, 3D printing. This is an additive technique that relies on the deposition of different layers of ingredients. Researchers have developed ODFs using 3D printing techniques, and in the final step of production the resultant is formed by the solidification of powder material or semi-solid material or by liquid materials. In 3D printing methods, extrusion technologies with fused deposition are the

commonest means of developing drug delivery systems. One example of this method is the fabrication of aripiprazole ODFs. Initially, aripiprazole filaments are prepared by hot-melt extrusion then mixed with PVA and moistened with ethanol before drying. The film filaments are prepared using an extruder. The blended powder is fed and extruded through the die at a constant speed. The film filament is then collected and further used to fabricate 3D-modeled ODFs. The fabricated ODFs have specific lengths, widths, and depths.

CHALLENGES IN FORMULATING FAST DISSOLVING ODF[16,17,18,19,20]

Huge literature is available on formulation, development and evaluation of oral fast dissolving or fast disintegrating tablets and films. However, formulator comes across with some challenges while development of such dosage forms. There is need to address such challenges which may help in future to explore the area in research and that may help in overall formulation and development. These challenges are directly related to patient compliance. Hence, preference should be given to them in formulation and development.

Following are some of the challenges in formulating fast dissolving oral film and trying to elaborate and solve these problems.

1) Insolubility of drug.
2) Taste masking of bitter and obnoxious drug.
3) Reduction in drying time of film.
4) High dose incorporation in film.
5) Stability of film against humidity and temperature.
6) Need special packaging.
7) Dose uniformity.

1. Insolubility of drug

Solubility plays a rate limiting parameter to get desired concentration of drug of orally administered formulation in systemic circulation.[7] Problem of solubility is a main challenge for formulation of oral film of BCS class II drugs having low solubility and high permeability. It is the most important preference of a drug candidate to be selected for formulation of oral film. In case of oral film, solubility plays an important role in two stages i.e. solubility of drug in solvent during formulation and solubility or dissolution of drug in saliva after putting the film in oral cavity. So, the solubility behaviour of drug remains one of the most challenging aspects in formulation of oral film.

2. Taste masking of bitter and obnoxious drug

Taste is an important parameter in case of fast dissolving oral film. Oral film must remain in contact with oral mucosa until it completely dissolves in saliva in oral cavity. For this, taste of bitter drugs should be masked. So, taste masking becomes a prerequisite for bitter drugs used in fast dissolving oral film to improve the patient compliance especially in the paediatric and geriatric population. Taste is the ability to respond to dissolved molecules and ions- "gatekeeper to the body." Human uses taste receptor cells that are clustered into onion-shaped organs called taste buds for detection of taste. A taste bud contains a pore which opens out to surface of the tongue and passing molecules and ions into the mouth to reach to the receptor cells inside. Human have around 10,000 taste buds which appear in foetus at about three months. A single taste bud bears 50-100 taste cells and each taste cells have receptors on its apical surface. These are trans-membrane proteins which bind to the molecules and ions that give rise to the four primary taste sensations namely - salty, sour, sweet and bitter. Recently, a fifth basic taste umami has been discovered. The umami is the taste of certain amino acids (e.g. monosodium glutamate).

3. Reduction in drying time of film

Drying time plays an important role in oral film formulation and in case of rate of production of oral film in industries. Generally, hot air oven is not used for drying of oral film of thermolabile drugs. So, oral film is dried at room temperature. But it takes more time to dry (about one day).

Panchal M. S. *et.al.* (2012) has reported that time taken by formulation for drying was found to be 24 hours at room temperature for the formulation of mouth dissolving film of Ropinirole hydrochloride prepared by using Pullulan polymers.

35°C temperature for 12 hours was used by Jadhav S. D. *et.al.* (2012) for drying fast dissolving oral film of Levocetirizine Dihydrochloride.

Time taken by formulation for drying was found to be 24 hours at 50°C for the formulation of fast dissolving oral film of Salbutamol Sulphate investigated by Prasanthi N. L. *et.al*. (2011).

Another temperature conditions were used by Prasanna D. *et.al.* (2012) which reported that time taken by formulation for drying was found to be 24 hours at 60°C for the formulation of fast dissolving oral film of Zolmitriptan.

4. High dose incorporation in film

Dose of drug in oral film formulation can be increased by increasing area of container. Only area should be increased keeping thickness of formulation solution constant so that volume of solution needed for formulation is also increased which help in incorporation of high dose and reduction in drying time also. Volume of formulation solution needed is calculated by following formula. If petri dish is considered as a container, then volume of formulation solution is given below.

Volume of formulation solution = area of petri dish × depth of formulation solution in dish

= x 0.35 cm

Volume of formulation solution = 0.35 cm^3

From literature survey, the highest dose to be incorporated in fast dissolving oral film is found to be 62.5 mg for the formulation of Simethicone oral film. Dose of drug incorporated in oral film was found to be in the range of 2 – 62.5 mg. High dose of drug can be incorporated in oral film by increase in film, increase in solubility of drug in formulation.

5. Stability of film against humidity and temperature

Fast dissolving oral film consists of about 45% of polymer which is hydrophilic in nature. In the humid atmosphere, film will absorb water and get liquefied due to dissolution of film in water. So, the stability of film against humidity is very difficult and challenging task. Amorphous drugs often have higher dissolution rates than their crystalline forms, but lower physical stability during storage. Addition of crystallisation inhibitors such as hydrophilic polymers to the amorphous drug to form a film formulation is the best method to prevent drug crystallisation. In the film formulation, polymers can decrease the molecular mobility of the drug, therefore reducing driving force of crystallisation and improving the physical stability of the amorphous drugs. If the API is freely soluble in the polymer, then the system should have excellent physical stability. If the API is not freely soluble in the polymer and is present at a supersaturated concentration, then stability is an issue.

6. Need special packaging

In the pharmaceutical industry, it is vital that the package selected adequately preserve the integrity of the product. A variety of packaging options are available for fast dissolving films. An aluminium pouch is the most used packaging material. APR-Labtech developed the Rapid card, patented packaging system designed for the Rapid films. The rapid card has same size as a credit card and holds three rapid films on each side. Every dose can be taken out individually.

Figure 3: ODF packaging.

7. Dose uniformity

Film which is to be made in a container must be cut into desired area containing required dose of drug. So, to get a uniform dose in all films which cut into desired area is a challenging task.

EVALUATION OF ORODISPERSIBLE FILMS[21,22]

ODFs formulations must be evaluated for the following evaluation test.

Visual Inspection

The prepared films are visually observed for colour, transparency, and homogeneity to assess some organoleptic properties.

Thickness

Thickness can be measured using vernier callipers. The thickness must be measured at three locations (one at centre and four corners of the film), and the mean thickness is calculated. Samples with air bubbles, nicks and having mean thickness variation of greater than 5% are excluded from analysis.

Weight Variation

Films 2 × 3 cm^2 in size are weighed on an electronic balance. The measurements are carried out in triplicates.

Folding Endurance

This gives an indication of the brittleness of the film. The film is repeatedly folded in the same spot until it broke. The folding endurance is taken as a function of the

number of times the film is folded before breakage. The experiment is done in triplicates and the mean ±SD is calculated.

Tensile Strength

Tensile testing is conducted using the modified method. The film is cut into 30 × 20 mm strips. Each test strip is stick on the surface of Glass slide with the help of Feviquick. Initial grip separation is 20 mm. The test is considered concluded when the film breaks. Tensile strength is computed with help of load require to break the film and cross-sectional area to evaluate tensile properties of the films. Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be calculated by dividing the maximum load by the original cross-sectional area of the specimen and it was expressed in force per unit area (MPa). Typical tensile strength for film is1.80± 0.20MPa.

Tensile strength (N/mm^2) = breaking force (N)/cross-sectional area of sample (mm^2)

Percentage Elongation (% E)

When stress is applied the film sample stretches and is referred to as strain. Strain is basically the deformation of the film divided by the original dimension of the film. Generally, elongation of the film increases as the plasticizer concentration increases. Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement by using the following formula;

Percentage elongation = $[L - L0] \times 100 / L0$

where L = final length and $L0$ = initial length. The estimations were carried out in triplicate.

Disintegration Time

The *in vitro* disintegration time of the formulations can be determined by petri dish method. About, 2 ml simulated saliva (pH 6.8) is placed in a clean dry petri dish and the film (2 X 2 cm) must be placed on its surface. The time required for the complete disintegration of the film is noted as the disintegration time. The test is performed on three strips of each formulation batch and mean ± SD is calculated.

Drug content uniformity

The optimized film of specific area (2 X 2 cm) must be cut and transferred to a graduated flask containing 100 ml of simulated salivary fluid pH 6.8 and stirred on a magnetic stirrer for 4 h. The solution was then filtered using a Whatman® filter paper. The filtered solution was diluted using the simulated salivary fluid. The absorbance is measured using UV spectrophotometer at appropriate λ max.

In vitro drug release

The optimized films of known weight and dimension (2 X 2 cm) are placed in a beaker containing 20ml of simulated salivary fluid (pH 6.8) as the dissolution medium maintained at 37±0.5°C. The medium must be stirred at 100 rpm. Aliquots (5 ml) of samples are taken at 5sec time intervals, and the same volume of fresh phosphate buffer is replaced. Samples are filtered, diluted suitably, and analysed using UV/Visible spectrophotometer at required λmax. The cumulative percentage drug release is calculated and plotted against time (sec).

CONCLUSION

ODFs continue to be an exciting area of pharmaceutical innovation, with the potential to revolutionize drug delivery for a diverse spectrum of therapeutic uses. ODFs represent a versatile and patient-friendly dosage form that has gained significant attention in the pharmaceutical industry. Recent advancements in the formulation of ODFs, including the incorporation of nanoparticles, have opened new avenues for enhancing drug delivery efficiency and expanding the range of drugs amenable to this administration route. However, further research and development are still needed to address the challenges related to taste masking, solubility, stability, and the incorporation of complex active ingredients.

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