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ORALLY DISSOLVING FILMS: A NOVEL APPROACH TO ORAL DRUG DELIVERY SYSTEM

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ABSTRACT

Over the past few decades, tendency toward innovative drug delivery systems has majorly increased attempts to ensure efficacy, safety and patient acceptability. As discovery and development of new chemical agents is a complex, expensive and time consuming process, so recent trends are shifting toward designing and developing innovative drug delivery systems for existing drugs. Out of those, drug delivery system being very eminent among pediatrics and geriatrics is orally disintegrating films (ODFs). These fast disintegrating films have superiority over fast disintegrating tablets as the latter are associated with the risks of choking and friability. This drug delivery system has numerous advantages over conventional fast disintegrating tablets as they can be used for dysphasic and schizophrenic patients and are taken without water due to their ability to disintegrate within a few seconds releasing medication in mouth. Various approaches are employed for formulating ODFs and among which solvent casting and spraying methods are frequently used. Generally, hydrophilic polymers along with other excipients are used for preparing ODFs which allow films to disintegrate quickly releasing incorporated active pharmaceutical ingredient (API) within seconds[1]. Orally disintegrating films have potential for business and market exploitation because of their myriad of benefits over orally disintegrating tablets. This present review attempts to focus on benefits, composition, approaches for formulation and evaluation of ODFs.

INTRODUCTION

Oral route of drug administration is a most preferred route due to its ease of administration, non-invasiveness, adaptability, patient compliance and acceptability. Regarding oral route of drug administration, many substitutes have continuously been presented by using recent novel technologies for pediatrics, geriatrics, nauseous and non-compliance patients. Bioadhesive mucosal dosage forms including adhesive tablets, gels and patches are outcomes of technological development. Among various dosage forms, the use of polymeric films for delivering medication into buccal cavity has developed great potential in recent era . Orally disintegrating films (ODFs), when placed on tongue, immediately hydrates by soaking saliva following disintegration and/or dissolution releasing active pharmaceutical agent from the dosage form ODFs are kind of formulations which are commonly prepared using hydrophilic polymers enabling rapid dissolution upon contact with saliva. Oral disintegrating tablets (ODTs) and oral disintegrating films (ODFs) are the typical examples of orally disintegrating drug delivery systems. These systems were developed in late 1970 to serve as an alternative to conventional dosage forms, for instance, fast disintegrating tablets and capsules for geriatrics and pediatric patients having difficulty in swallowing conventional dosage forms. A typical ODF is usually equal to the size of a postage stamp. In market place, the introduction of ODT was strongly associated with counseling of patients about the appropriate administration by giving instruction like “do not chew/do not swallow”. However, in spite of these instructions, incidents regarding chewing and swallowing were often reported [2]. But, ODFs untied the masses from these adverse events. The administration of ODFs has numerous advantages and some of them are as follows:

- Easy transportation.
- Ease of swallowing for geriatrics and pediatrics.
- Convenient and accurate dosing.
- No need of water for administration.
- Convenient for dysphasic patients having difficulty in swallowing tablets and capsules.
- Rapid onset of action with increased bioavailability due to bypassing hepatic first pass effect and stability
- No expensive lyophilization
- High mechanical strength
- Rapid disintegration
- Reduced choking risks are the quality attributes of ODFs .

ODFs have attained remarkable significance in pharmaceutical industry for the reason of possessing unique properties and fast disintegration time ranging from seconds to one minute.

High temperature and moisture sensitivity necessitating expensive packaging and inability of high dose loading are some disadvantages of ODFs[3].

Classification of Fast Dissolving Technology

For ease of description, fast – dissolve technologies can be divided into three broad groups[4]:

1. Lyophilized systems **:**

   The technology around these system involves taking a suspension or solution of drug with other structural excipients, through the use of a mould or blister pack, forming tablet shaped units. The units or tablets are then frozen and lyophilized in the pack or mould. The resulting units have very high porosity, which allows rapid water or saliva penetration and very rapid disintegration**.**

2. Compressed tablet – based systems **:**

   This system is produced using standard tablet technology by direct compression excipients. Depending on the method of manufacture, the tablet technologies have different levels of hardness and friability. The speed of disintegration for fast dissolve tablets compared with a standard tablet is achieved by formulating using either water soluble excipients Superdisintegrant or effervescent components, to allow rapid penetration of water into the core of the tablet**.**

3. Thin oral film

   Oral films also called oral wafers, evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products. Today, FDFs are proven and accepted technology for the systemic delivery of APIs for over – the counter (OTC) medication and are in the early – to mid development stages for prescription drugs.

This has been attributed to the success of the breath freshener products by consumers such as Listerine Pocket packs in the US consumer market. Such systems use a variety of hydrophilic polymers to produce a 50200 mm film. The film is manufactured as a large sheet and then cut into individual dosage units for packaging[5].

Structural Features of Oral Mucosa Structure

The oral mucosa is composed of an outmost layer of strafied squamous epithelium. Below this lies a basement membrane, a lamina porpria followed by the sub mucosa as the the inner most layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that is has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cell are shed from the surface of the epithelium considerably more permeable to water than keratinized epithelia[6].

Composition of Oro-mucosal Region

Oro-mucosal Cell: Are made up of proteins and carbohydrates. It is adhesive in nature and acts as a lubricant, allowing cell to move relative to one another, while the mucosal with less friction. The mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery. In other part of body mucus is synthesized and secreted by the goblet cells, however in the oral mucosa; mucus is secreted by the major and minor part of saliva. Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands.

Formulation

Mouth dissolving film is a thin film with an area of 5 -20cm2 containing an active ingredient. The immediate dissolution, in water or saliva respectively, is reached through a special matrix from water-soluble polymers.formulation considerations (plasticizers etc.) have been reported as important factors affecting mechanical properties of the films, such as shifting the glass transition temperature to lower temperature[7].

Composition of the Formulation –

A typical composition contains the following:

a) Drug – 5% to 30% w/w.
b) Water soluble polymer – 45%w/w
c) Plasticizers – 0-20%w/w
d) Sweetening agent- 3% to 6% w/w.
e) Saliva stimulating agent – 2 to 6% w/w
f) Fillers, Colors, flavor surfactant etc. q.s.

1) Drugs

Several class of drugs can be formulated as mouth dissolving films including antiulcer (e.g. omeprazole), antiasthamatics (salbutamol sulphate), antitussives, expectorants, antihistaminics, NSAID'S (e.g. paracetamol, meloxicam, valdecoxib),antihypertensives etc .

2) Water soluble polymers

Water-soluble polymers are used as film formers. The use of film forming polymers in dissolvable films has attracted considerable attention in medical and nutraceutical application[8]. The water-soluble polymers achieve rapid disintegration, good mouthfeel and mechanical properties to the films. The disintegration rate of the polymers is decreased by increasing the molecular weight of polymer film bases. Some of the water soluble polymers used as film former are HPMC E-3 and K-3, Methyl cellulose A-3, A-6 and A-15, Pullulan, carboxmethylcellulose cekol 30, Polyvinylpyrollidone PVP K-90, Pectin, Gelatin, Sodium Alginate, Hdroxypropylcellulose, Polyvinyl alcohol, Maltodextrins and EUDRAGIT RD 108,9,10,11,12 .Polymerized resin is a novel film forming polymer .

3) Plasticizers

Formulation considerations (plasticizer, etc.) have been reported as important factors affecting mechanical properties of films. The mechanical properties such as tensile strength and elongation to the films have also been improved by the addition of plasticizers. Variation in their concentration may affect these properties. The commonly used plasticizers are glycerol, di-butylpthallate, and polyethylene glycols etc .

4) Surfactants

Surfactants are used as solubilising or wetting or dispersing agent so that the film is getting dissolved within seconds and release active agent immediately. Some of the commonly used are sodium lauryl sulfate, benzalkonium chloride, bezthonium chloride, tweens etc. One of the most important surfactant is polaxamer 407 that is used as solubilizing, wetting and dispersing agent .

5) Flavour

Any flavor can be added to improving the formulation acceptance. such as intense mints, sour fruit flavors or sweet confectionery flavors .

6) Colour

A full range of colors is available, including FD&C colors, EU Colours, Natural Colours and custom Pantone-matched colours

7) Saliva stimulating agents

May also be added to enhance the disintegration and to get rapid release. Some of these agents are citric acid, tartaric acid, malic acid, ascorbic acid and succinic acid .

MANUFACTURING METHODS

One or combination of the following process can be used to manufacture the mouth dissolving films[9]

i) Solvent casting
ii) Semisolid casting
iii) Hot melt extrusion
iv) Solid dispersion extrusion
v) Rolling method

1) Solvent casting method

In solvent casting method water soluble polymers are dissolved in water and the drug along with other Excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the Petri plate and dried.

2) Semisolid casting

In semisolid casting method firstly a solution of watersoluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film is about 0.015-0.05 inches. The ratio of the film is about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

3) Hot melt extrusion

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally the melt is shaped in to films by the dies. There are certain benefits of hot melt extrusion . -Fewer operation units -Better content uniformity -An anhydrous process

4) Solid dispersion extrusion

In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies.

5) Rolling Method

In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cutted in to desired shapes and sizes.

Advantages of Buccal Films

The design of thin film are often referred to as PharmFilm, this oral drug delivery technology offers several advantages over other modes of drug delivery, such as ingestible tablets, chewable tablets, orally dissolving tablets, soft gels, liquids or inhalants.The and sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing, and enhance the efficacy and safety profile of the medicament[10].

1. All tablet dosage forms, soft gels and liquid formulations primarily enter the blood stream via the gastrointestinal tract, which subjects the drug to degradation from stomach acid, bile, digestive enzymes and other first-pass effects. As a result, such formulations often require higher doses and generally have a delayed onset of action. Conversely, buccal and sublingual thin-film drug delivery can avoid these issues and yield quicker onsets of action at lower doses.
2. Thin film is more stable, durable and quick dissolving than other conventional dosage forms.
3. Thin film enables to improve dosage accuracy relative to liquid formulations ,since every strip is manufactured in such a way that it contains a precise amount of the drug.
4. Buccal films not only ensures more accurate administration of drug, but also can improve compliance due to the intuitive nature of the dosage form and its inherent ease of administration. These properties are especially beneficial for pediatric, geriatric , unconscious patients and neurodegenerative disease patients where the complete dosage form is different..
5. Buccal films has the ability to dissolve rapidly without the need for water, which provides an alternate way to the patients to swallow and to patients suffering from n6. Buccal films drug delivery has the potential to allow the development of sensitive drug targets that may not be possible in tablet or liquid formulations.
7. From a commercial perspective thin film drug delivery technology offers an opportunity to extend revenue lifecycles for pharmaceutical companies whose drug patent is expiring and will soon be vulnerable to generic competition.
8. It also avoids the risk and inconveniences of intravenous therapy.
9. Bypass the variation in the absorption and metabolism association with the oral administration.
10. Permits continuous drug administration and the use of drugs with a short biological half-life.
11. Increase the bioavailability and efficacy of the desire of the physician
12. Most of the time lower dose is sufficient.

13. Permits a rapid termination of the medication, if needed, by simply removing the buccal film from the mouth.

14. Patients suffering from dysphasia, repeated emesis, motion sickness and mental disorders prefers this dosage form as they are unable to swallow large quantity of water.

15. However,there are some limitations too, the most prominent amongst which is the realization that only a small percentage of the drugs, can be delivered through buccal delivery system.

16. The disadvantage of the most ODT is that they are fragile and brittle, which warrants special package for protection during storage and transportation. Since the films are flexible they are not as fragile as most of the ODTs. Hence, there is a ease of transportation and during consumer handling and storage.

17. Sublingual film delivers a convenient, quick-dissolving therapeutic dose contained within an abuse-deterrent film matrix that cannot be crushed or injected by patients, and rapidly absorbs under the tongue to ensure compliance, such as those patients receiving chemotherapy.

Ideal Characteristics Of A Drug To Be Selected For Fast Dissolving Drug Delivery System

- Drug requires no water fororal administration for dissolve/disintegrate in mouth in a matter of seconds.
- Drug should have pleasant taste.
- Have an acceptable taste masking property.
- Be harder and less fragile.
- The Incorporated drug should have low dose less than 30mg.
- The drugs with smaller and moderate molecular weight are preferable.
- Drug should have good stability and solubility in water as well as in saliva
- Exhibit low sensitivity to environmental conditions (temperature and humidity).
- The drug should be partially unionized at the pH of oral cavity.
- The drug should have the ability to permeate oral mucosal tissue.
- Leave minimal or no residue in mouth after administration.
- Allows the manufacture of tablet using conventional processing and packagingequipments.

PREPARATION OF MOUTH DISSOLVING FILMS

Method of preparation of Film:

The preparation of film was done by using solvent casting method. The polymer was dissolved in hot water. The drug and other excipients were dissolved in ethanol. This solution was added to the polymeric solution. Then the solution was mixed by using mixing device for 45 minutes with rotating speed 60-80 rpm. The entrapped air is removed by vacuum. The resulting solution was

casted slowly and with continuous flow on glass plate. The plates were kept in a hot air oven at 60 for 24 hours. Dried film was gently separated from glass plate, cut into sizes of about 4 cm2.

EVALUATION TESTS

Thickness:

As the thickness of film is directly concern with drug content uniformity so it is necessary to ascertain uniformity in the thickness of the film. It can be measured by micrometer screw gauge or calibrated digital vernier Calipers at different strategic locations.

Surface pH

The film to be tested was placed in a petridish and was moistened with 0.5 ml of distilled water and kept for 1hr. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and kept for 1 min to allow equilibrium condition.

Dissolving time

The dissolving time was determined by placing the film in a beaker containing 50 ml of phosphate buffer (pH 6.8). Time required by the film to dissolve completely was noted.

Drug content estimation

A circular film of 2.5cm diameter was cut and placed in a beaker containing 100 ml of phosphate buffer pH 6.8 solutions. The contents were stirred in magnetic stirrer to dissolve the film and the contents were transferred to a 100ml volumetric flask. The absorbance of the solution was measured against the corresponding blank solution at 273 nm. As the absorbance noted above 1mcg/ml, 1ml of the stock was further diluted to 10ml of phosphate buffer solution (pH6.8) and absorbance was measured at 273nm[12].

Dryness Test / Tack Tests:

About eight stages of film drying process have been indentified and they are set – to touch, dust – free, tack – free (Surface dry), Dry – to touch, dry – hard, dry – through (dry – to – handle), dry-to-recoat and dry print – free. Although these tests are primarily used for paint films most of the studies can be adapted intricately to evaluate pharmaceutical OFDF. The details of evaluation of these parameters can be checked elsewhere and are beyond the scope of this review track is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip. Instruments are also available for this study[13].

Disintegration time It was determined by using disintegration test apparatus. 5cm2 film was placed in the basket, raised and lowered it in such a manner that complete up and down

movement at a rate to achieve equivalent to thirty times a minute. Time required by the film to achieve no trace of film remaining above the gauze was noted.

In-vitro drug dissolution studies

The dissolution studies were conducted using phosphate buffer pH 6.8 . Each film strip (containing drug equivalent to 5 mg) was then submerged into the dissolution medium. The dissolution study was carried out using dissolution test apparatus USP type-II at 370C, at 50 rpm, using 900 ml phosphate buffer (pH 6.8) as dissolution medium. Test samples were withdrawn at different time intervals and analyzed spectrophotometrically at 273 nm.

Weight Variation of The Film

Weight variation was studied by individually weighing 6 randomly selected film strips. Average weight of films calculated. The weight of each film should not deviate significantly from average weight.

Tensile Strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross – sectional area of the strip as given in the equation below: 30Tensile Strength = Load at breakage.

Strip Thickness x Strip width

Percent Elongation

When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally elongation of strip increase as the plasticizer content increase % Elongation = Increase is length x 100 / Original length

Folding Endurance

It is measured manually for the prepared oral film. A film was repeatedly folded at 180˚ at the same place till it breaks. This test was performed on three films of each formulation and mean ±SD was calculated.

Percentage Moisture Loss(Pml):

Percentage moisture loss was also carried to check the integrity of films at dry condition. Three 2cm diameter films was cut and weighed accurately and kept in desiccators' containing fused anhydrous calcium chloride. After 72 hours the films were removed and weighed. Average percentage moisture loss of three films was found out.

Young's modulus

Young's modulus or elastic modulus is the measure of stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

Hard and brittle strips demonstrate a high tensile strength and Young's modulus with small elongation.

Fourier Transformed Tear Resistance:

Tear resistance of plastic film or sheeting is a complex function of its ultimate to rupture. Basically very low rate of loading 51 mm (2 in) / min is employed and is designed to measure the force to initiate tearing. The maximum stress or force (that is generally found near the onset of tearing) required to tear the specimen is recorded as the tear resistance value in Newton's (or pounds – force) Infrared Spectroscopy

The different formulation prepared was scanned for infrared spectroscopy.

For the scanning of the sample the longer wavelength from 500 cm-1 to 4000 cm-1 was used .

Transparency:

The transparency of the films can be determined using a simple UV spectrophotometer. Cut the film samples into rectangles and placed on the internal side of the spectrophomoter call. The determine transmittance of films at 600 nm. The transparency of the films was calculated as follows:

Transparency = (log T600) / b = Where T 600 is the transmittance at 600 nm and b is the films thickness (mm) and c is concentration

Scanning Electrone Microscopy(Sem)

The formed different samples were cut into size of 2x2 cm2 and stored to avoid brittleness such formed films were collected and evaluated for SEM analysis .The samples were coated with gold film (of thickness 200nm) and visualized under reduced pressure .

CONCLUSION

Fast dissolving oral films have several advantages over the conventional dosage forms. So they are of great importance during the emergency cases whenever immediate onset of action is desired. Fast dissolving drug delivery systems have better patient compliance and may improve biopharmaceutical properties, improves efficacy and better safety, compared with conventional oral dosage forms. After the Fast dissolving tablets , the new products as Fast dissolving oral films are intended for the application in the oral cavity and they are innovative and promising

dosage form especially for use in elder patients. The development of fast dissolving drug products also provides an opportunity for a line extension in market place, a wide range of drugs (e.g. NSAIDS, antiulcer, antihistamine, Hypnotics & sedatives, antipsychotics, antiparkinsonism, antiemetic, antimigrane and antidepressants) can be considered for this dosage form. In future, this system is most acceptable and prescribed due to its quick action. i.e. within a minute. Because of increasing patient demand, popularity of these dosage forms will expand the study in future[14].

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