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A Noval Approach of Fast Dissolving Films: A Review

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Abstract

The main objective of proposed work is to enhance the bioavailability of selective drug by rapid dissolving films techniques. Rapidly dissolving films (RDF) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improves the efficacy of active pharmaceutical ingredients (API) by dissolving within minute in oral cavity after the contact with saliva without chewing and no need of water for administration. Rapidly dissolving films also have an established shelf-life of 2-3 years depending on the API but are extremely sensitive to environmental moisture. The oral thin-film technology is still in the beginning stages and has bright future ahead because it fulfils all the need of patients. Eventually, film formulations having drug will be commercially launched using the RDF technology. Excipients are film forming polymers, plasticizers, sweetening agents, saliva stimulating agents, flavorings and colouring agents. Various methods are available for the preparation of rapid dissolving films such as solvent casting, hot melt extrusion, semisolid casting, solid dispersion extrusion and rolling method. Characterization parameters for rapidly dissolving films are thickness, appearance, weight variation, disintegration time, drug content, tackiness, surface $p^{H.}$.
Keywords: surface p^{H}, Excipients, Rapidly dissolving films, colouring agents.

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1. Introduction

Pharmaceutical science and technology has progressed enormously in the recent years. These advances in therapeutics and the need to optimize drug delivery in the body have increased the value of dosage form in therapy. This increased awareness has resulted in an increased sophistication and level of expertise in the design, development, manufacture, testing and regulation of drugs and dosage forms. Despite tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because of the low cost and the ease of administration which in turn has increased the level of patient compliance. Many pharmaceutical dosages are administered in the form of pills, granules, powders, and liquids. Generally, a pill is designed to swallow or chew so as to deliver a precise dosage of medication to patients. The pills, which include

tablets and capsules, are able to retain their shapes under moderate pressure. However, some patients, particularly pediatric and geriatric patients, have difficulty in swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking.

Patient convenience and compliance oriented research has resulted in bringing out safer and newer drug delivery systems. Recently fast dissolving drug delivery systems have started gaining popularity and acceptance due to their rapid disintegration and ease of administration. Keeping such pediatric and geriatric patients in mind, several fast-dissolving drug delivery systems have been developed. Fast-dissolving drug delivery was pioneered by scientists at Wyeth Laboratories in the UK during the late 1970s. Most of the existing fast-dissolving drug delivery systems are in the form of solid tablets and films or strips which are designed to dissolve/disintegrate in the patient's mouth within a few seconds or minutes. Fast dissolving drug delivery is an emerging novel technique in the pharmaceutical industry which offers a convenient way of delivering medication, for all generation.An ideal fast-dissolving delivery system should have the following properties: high stability, transportability, ease of handling and administration, no special packaging material and/or processing requirements, no water is required for administration, and should have pleasant taste.

Table1: Salient features and advantages of fast dissolving buccal films

Special features	Advantages
Thin elegant film	Convenient dosing
Various sizes and shapes	No water needed
Unobstructive	No risk of chocking
Mucoadhesion	Taste masking
Fast disintegration	Enhanced stability
Quick dissolving	Improved patient compliance
Rapid release	Life cycle management

Normally these films are soluble in water at room temperature and will break up in 30 sec and disappear in one minute. The faster the drug goes into the solution, quicker its absorption and onset of clinical effect. By altering the condition and formulation factors, it is possible to slow down or speed up dissolving rate in the mouth. The mouth dissolving films-contain active ingredients, flavors, sweeteners and other ingredients, which are released as the film dissolves.

These films dissolve instantaneously when placed on the tongue and are also called as Orally Dissolving Films (ODFs). Most people are familiar with ODFs in the form of breath freshening strips or cough suppressants. However, the drug delivery advantages and healthcare benefits of this dosage form extend far beyond these applications. A major claim of the some ODFs is increased bioavailability compared to traditional dosage form. Because of dispersion in saliva while still in the oral cavity, there can be pre-gastric absorption from some formulations in those cases where the drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption of the many formulations. However, other formulations show nearly identical plasma-concentration profiles. Any pre-gastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo a great deal of hepatic metabolism. However, if the amount of swallowed drug varies, there is the potential for inconsistent bioavailability. While the claimed increase in bioavailability is disputable, it is clear that the major advantage of these formulations is convenience.

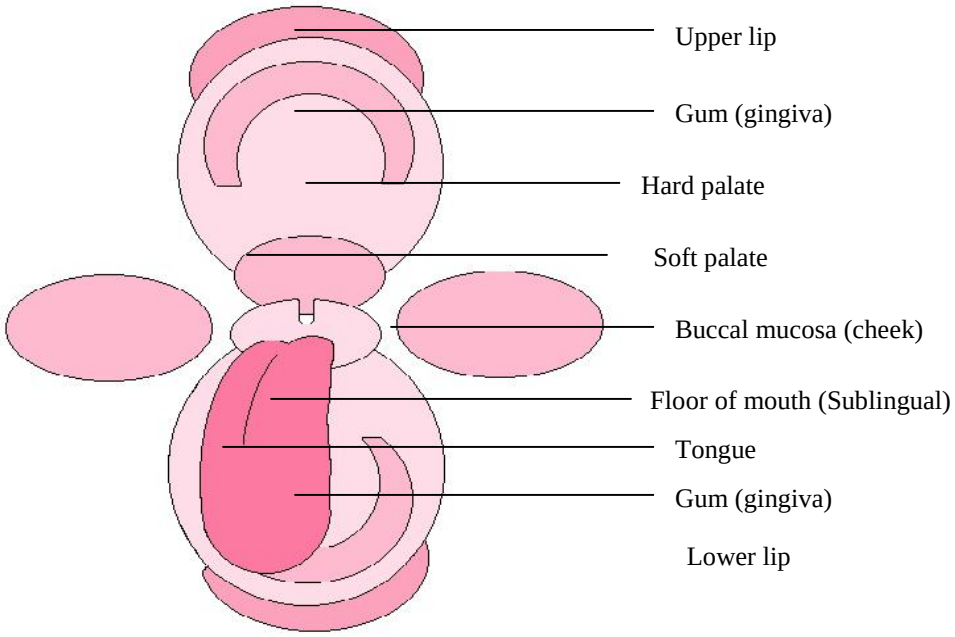
Following are the characteristics of the mouth dissolving film [3, 4]:

1. Require no water for the administration (to swallow).
2. Dissolve or disintegrate in the mouth in few seconds.
3. Possess pleasant taste, high stability and transportability.
4. Leave minimal or no residue in the mouth after administration.
5. Need no special packaging materials or processing requirements.

Advantages of mouth dissolving films [2, 3]:

1. The film alleviates fear of throat choking.
2. The film is easy to handle and administer.
3. The film maintains a simple and convenient packaging.
4. The film alleviates unpleasant taste and is easy to manufacturer.
5. This system allows children, elderly and the general population to take their medication directly wherever and whenever needed.
6. The fast dissolving action is primarily due to the large surface area of the film.

7. The films are tough, solid, soft, flexible and do not require special packaging.
8. The films are thin and can be carried in a patients pocket and wallet.
9. The films enhance stability of some formulations.



The oral mucosa tissue consists of a multilayered epithelium covered with mucus and consists of a stratum distendum, stratum filamentosum, and stratum suprabasale and stratum basale. Below this lies a basal lamina. The basal lamina connects the epithelium to a connective tissue layer, the lamina propria. Below lamina propria lies submucosa. Epithelium serves as the mechanical barrier that protects underlying tissues where as lamina propria acts as a mechanical support and also carries blood vessels and nerves.

The epithelium of human oral mucosa shows several distinct patterns of maturation, related to the functional demands of the tissue. Some regions of the epithelium are keratinized (dehydrated, mechanically tough and chemically resistant), where as others are not. Keratinized epithelium is found in less flexible masticatory mucosa of gingival and part of hard palate. Nonkeratinized (flexible) epithelium forms the surface of the distensible lining of mucosa of the soft palate, floor of the mouth, lips and cheek. The nonkeratinized regions, such as buccal mucosa, are more permeable than the keratinized regions. This is due to some extent, to the composition of intercellular lipids comprising the particular region. Whereas keratinized regions contain predominantly neutral lipids (ceramides), nonkeratinized areas are composed of glycosyl ceramide that appears to be derived from membrane coating granules of keratinized tissue.

1.2 The membrane coating granules (MCG) [6]:

As cells of epithelium mature, small organelles, known as membrane coating granules (MCG), probably derived from the golgi complex appear in the prickle cell layer. In later stages of differentiation, they migrate towards the superficial part of the cell at the junction of the granular and cornified layers in the keratinized tissues; and in the deeper part of the superfacial cell layer in the nonkeratinized tissue. The bounding membrane fuses with the cell membrane, and the contents of the granules are discharged into the intercellular space. During fusion, the bonding membrane of the granules is introduced into the plasma membrane of the epithelial cell. The extruded material, composed primarily of lipid is then organized into multiple stacked lipid sheets. MCG of keratinized oral epithelium are ovoid, 0.1-0.3μm in length and have high ratio of lipid to protein. The lipids include phospholipids, cholesterol esters, fatty acids, ceramides and several other natural lipids. In nonkeratinized epithelium, MCG have similar distribution within the epithelium and similar chemical composition to those of keratinized tissue. They are spherical, approximately 0.2 μm in diameter.

A relationship between MCG and permeability has been established, thus, a greater volume of MCG is associated with a lower permeability. Lipids including small amounts of ceramides, monohexosylceramides, cholesterol esters, cholesterol sulphate and fatty acids and a high proportion of phospholipids, triglycerides and cholesterol fill in the

intercellular space of oral keratinized tissue. In nonkeratinized regions, the chemical nature of the intercellular material is less defined than that in the keratinized epithelium. Since the intercellular spaces of nonkeratinized epithelia appear to contain amorphous material, it is possible that the lipids within them are in a nonlamellar lipid phase, with only occasional short stacks of lipid lamellae. This may result in a barrier that is less efficient than that from, keratinized regions.

1.3 Saliva [6, 7]:

Saliva is the protective fluid for all the tissues of the buccal cavity and its necessary for oral health. Saliva protects soft tissues from abrasion by rough materials and from some chemicals. Upto 70 % of total mucin found in saliva is contributed by minor salivary glands. Main role of salivary mucin is in the non-immune protection of the oral cavity by acting as a lubricant and as a selective permeability barrier against drying. Saliva is 99% water and contains organic and inorganic materials. The surface of the oral cavity is constantly bathed with a stream of saliva (approximately 1 to 1.2 lit per day). The pH of whole saliva varies between 6.2-7.5.

1.4 Mechanisms involved in drug absorption across the oral mucosa [7, 8]:

The mechanisms by which drugs cross biological lipid membranes are passive diffusion, facilitated diffusion, active transport and pinocytosis. Small water-soluble molecules may pass through, small water filled pores. The main mechanism involved in drug transfer across the oral mucosa, is passive diffusion has also been shown to take place, primarily with nutrients. Passive diffusion involves the movement of a solute from a region of high concentration in the mouth to a region of low concentration within the buccal tissues. Further diffusion then takes place into the venous capillary system, with the drug eventually reaching the systemic circulation via the jugular vein. The physicochemical characteristics of a drug are very important for this diffusion process.

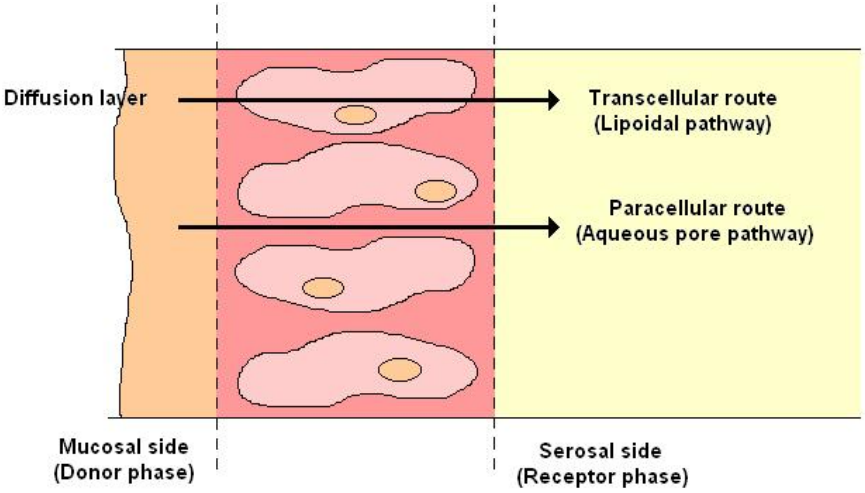


Figure 3: Drug absorption pathways across buccal mucosa

1.5 Advantages of buccal drug delivery system [8, 9]

1. Ease of administration.
2. Permits localization of the drug in the oral cavity for a prolonged period of time.
3. Offers excellent route for systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability.
4. A significant reduction in dose can be achieved, thereby reducing dose dependent side effects.
5. Drugs, which are unstable in acidic environment of the stomach or are destroyed by the enzymatic or alkaline environment of the intestine can be administered by this route.
6. The presence of saliva ensures relatively large amount of water for drug dissolution unlike the case of rectal and transdermal routes.
7. It offers passive system for drug absorption and does not require any activation.
8. It can be made unidirectional to ensure only buccal absorption.
9. The buccal mucosa is highly perfused with blood vessels and offers greater permeability than the skin.
10. Therapeutic serum concentrations of the drug can be achieved more rapidly.
11. Better patient compliance than vaginal, rectal and nasal route of administration.
12. Buccal mucosa is less prone to damage or irritation than nasal mucosa and shows short recovery times after stress or damage.
13. Termination of therapy is easy.
14. Can be administered to unconscious patients.

15. Increased patients compliance.

1.6 Disadvantages [10]:

1. Once placed at the absorption site, the dosage form should not be disturbed.
2. There is a possibility that patient can swallow the tablet.
3. The drug swallowed in saliva is lost.
4. Properties like unpleasant taste or odour, irritability to the mucosa, stability at salivary pH poses limitations to the choice of drug.
5. Only drugs with small dose can be administered.
6. Eating and drinking may become restricted.

Composition Of The Fast Disintegrating Film System [11, 12] :

Fast dissolving film is a thin film with an area of 5-20 cm^2 containing an active ingredient. The immediate dissolution, in water or saliva respectively, is reached through a special matrix from water-soluble polymers. Drugs can be incorporated up to a single dose of 15 mg. 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.

A typical composition contains the following

Table 2: Composition of the film

Ingredients	% w/w
Drug	1-25%
Water soluble polymer	40-50%
Plasticizers	0-20%
Fillers, colours, flavours, etc	0-40%

Formulation consideration [12, 13, 14]:

a. Active pharmaceutical ingredient
b. Film forming polymers
c. Plasticizer
d. Sweetening agent
e. Saliva stimulating agent
f. Flavoring agent
g. Coloring agent

Active pharmaceutical ingredient

A typical composition of the film contains 1-25% w/w of the drug. Variety of APIs can be delivered through fast dissolving films. Small dose molecules are the best candidates to be incorporated in rapidly dissolving film. Multivitamins up to 10% w/w of dry film weight was incorporated in the films with dissolution time of less than 60 seconds. It is always useful to have micronized API which will improve the texture of the film and also for better dissolution and uniformity in the rapidly dissolving film. Many APIs, which are potential candidates for rapidly dissolving film technology, have bitter taste. This makes the formulation unpalatable especially for pediatric preparations. Thus before incorporating the API in the rapidly dissolving film, 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.

Film forming polymer:

Since the primary use of all FDDS relies on their disintegration in the saliva of the oral cavity, the film that is formulated must necessarily be water soluble. In order to prepare a thin film formulation that is water-soluble, excipients or polymer must be water soluble with low molecular weight and excellent film forming capacity. The polymer employed should be non-toxic, non-irritant and devoid of leachable impurities. It should have good wetting and spread- ability property. The polymer should exhibit sufficient peel, shear and tensile strengths. The polymer should be readily available and should not be very expensive. The polymers can be used alone or in combination to improve hydrophilicity, flexibility and mouth feel and solubility characteristics of fast dissolving films.

The stiffness of the strip depends on the type of polymer and the amount of polymer in the formulation. Polyvinyl pyrrolidone films are brittle in nature and therefore Crosspovidone is mixed with poly vinyl pyrrolidone for preparation of flexible fast disintegrating films. Combination of microcrystalline cellulose and maltodextrin has

been used to formulate fast dissolving films of piroxicam made by hot melt extrusion technique. In this case, microcrystalline cellulose is used to render the film non-sticky and smooth. Microcrystalline cellulose is also used to decrease the disintegration time and improve the dissolution of drug from the films. Water soluble polymer that may be used include natural gums such as guar gum, xanthan gum, acacia, other available polymers are, polyethylene oxide, acrylic based polymer and several types of sodium carboxymethylcellulose (CMC), several types of hydroxypropylmethyl cellulose (HPMC), a synthetic copolymer of polyethylene glycol–polyvinyl alcohol and sodium alginate. Cellulose ethers are widely available and economical. Pullulan, an 1,6-linked maltotriose produced from the fungus *Aureobasidium pullulan*, has also been used. Five types' starches and maltodextrin have also been investigated as alternative film formers. The physicochemical characteristic of the polymers selected for film formulation play a vital role in determining the resultant disintegration time of the cast thin film oral dosage form.

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 also the type of solvent employed in the casting of film. 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 % 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 isomaltose 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, sucralose, Neotame and alitame have more than 200, 600 and 8000 time sweetening power respectively as compared to sucrose.

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. Eg: 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.

Flavoring agents:

Preferably up to 10% w/w flavors are added in the fast dissolving film formulations The acceptance of the oral disintegrating or dissolving formulation by an individual is largely depends on the initial flavor 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 flavor 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. Flavoring agents can be selected from synthetic flavor 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 flavor oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence type.

Coloring agents: FDA approved colourants are to be used at the concentration level of 1% w/w in FDDS

Methods of Manufacture of Fast Dissolving Films [15, 16, 17]:

- Solvent casting
- Hot-melt extrusion
- Semisolid casting
- Solid dispersion extrusion
- Rolling

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 moulds and dried.

2) **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.

Hot melt extrusion is commonly used to prepare granules, sustained release tablets, transdermal and transmucosal systems.

3) Semisolid casting:

In semisolid casting method firstly a solution of water-soluble 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 acid insoluble polymer to film forming polymer should be 1:4.

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.

Rolling Method:

In rolling method a solution or suspension of drug with film forming polymer is prepared and subjected to the roller. The solution or suspension should have specific rheological consideration. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cut in to desired shapes and sizes. In this method, the film is prepared by preparation of a premix, addition of an active ingredient and subsequent formation of a film.

2. Evaluation of Fast Dissolving Films

1. Appearance:

All the prepared films were checked for their transparency and opacity.

2. Weight variation:

Ten films were randomly selected and their average was calculated. Individual films were weighed and compared with the average weight for the deviation and results were tabulate.

3. Thickness

Thickness of the film was measured with screw gauge micrometer at different strategic locations. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip and results were tabulate.

4. Tackiness:

Six Films were randomly selected. Each strip was pressed against the fingertips and tackiness was recorded. Results were noted in qualitative terms as tack and non-tacky.

5. Folding endurance test:

Folding endurance of film was determined by repeatedly folding a small strip of film (1×1 cm^2) at the same place till it breaks is noted as the folding endurance value and results were tabulate.

6. Tensile strength:

Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be computed from the applied force at rupture as a mean of three measurements and the cross-sectional area of the fractured film as described in the equation and results were tabulate.

$$Tensile\ strength = \frac{\text{load at failure} \times 100}{film\ thickness \times film\ width}$$

7. Percent elongation:

When tension is applied to the film and film strip is starches this is a strain. If elongation of film increase means addition of plasticizer is increase and results were tabulate.

$$\%\ Elongation = \frac{\text{increase in length} \times 100}{original\ length}$$

8. Surface pH: The surface pH of fast dissolving film was determined in order to find out the possible any *in-vivo* side effect. A combined pH electrode was used for this purpose. Oral film was slightly wetted with water. The pH

was measured with the glass membrane electrode in contact with the surface of the oral film. The procedure was performed in triplicate and average with standard deviation was reported and results were tabulate.

9. Disintegration time:

The disintegration time was measured using modified disintegration method. For this purpose a petri dish was filled with 10 ml of water. The film was carefully put in the centre of petri dish. The time for the film to completely disintegrate in to fine particles was noted and results were tabulate.

10. Drug content: Drug content determination of the film was carried out by dissolving the film of 1 cm^2 in 100 ml of pH 6.8 phosphate buffer using magnetic stirrer for 1 hour. The drug concentration was then evaluated spectrophotometrically. The determination was carried out in triplicate for all the formulations and average with standard deviation was recorded and reported and results were tabulate.

3. Conclusion

Rapidly dissolving film is a promising approach with a view of obtaining faster action of the drug and would be advantageous in comparison to currently available conventional forms. The main objective of the study was to formulate and evaluate rapidly-dissolving film containing a drug. Prepared films were transparent with smooth surface and acceptable mechanical properties. There was no interaction between drug and polymer. Film was disintegrated in 42 seconds. Drug release was found to be 95% in 10 minutes. From the present investigation it can be concluded that rapidly dissolving film formulation can be a potential novel drug dosage form for pediatric, geriatric patients and also for general population.

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