FAST DISSOLVING ORAL DOSAGE FORM-AN OVERVIEW

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Submitted on: 15.11.2013; Reviewed on: 30.11.2013; Accepted on: 05.12.2013

ABSTRACT

Over the few decades, there have been increased interests to formulate the drug delivery system with advancement, improved safety and efficacy to patient. As increase in new drug moiety is quite expensive, so the main aim is to develop a new drug delivery system with the same drug as it produce its maximum therapeutic effect over conventional tablets. Fast dissolving tablets are disintegrating or dissolving in saliva without the need of water. Some tablets are designed to dissolve in saliva remarkably fast, within few seconds and are fast dissolving tablets. Mouth dissolving films are thin solid dosage form which when placed in the oral cavity; dissolve within few seconds without chewing and intake of water. This review article overview the advancement in the oral dosage form, application, formulation consideration, method of preparation, and evaluation of fast dissolving oral dosage form.

KEYWORDS: Oral films, Fast dissolving tablets, Buccal cavity, Oral dosage form.

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INTRODUCTION

Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. About 60% of all dosage forms available are the oral solid dosage form. The lower bioavailability, long onset time and dysphasia patients turned the manufacturer to the parenterals and liquid orals. But the liquid orals (syrup, suspension, emulsion etc) have the problem of accurate dosing mainly and parenterals are painful drug delivery, so most patient incompliance.

Each pharmaceutical company wants to formulate the novel oral dosage form which has the higher bioavailability, quick action and most patient compliance. So they formulate the fast dissolving tablets by using superdisintigrants and hydrophilic ingredients. Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. Fast dissolving oral films (FDOFs) are the most advance form of oral solid dosage form due to more flexibility and comfort. It improve the efficacy of APIs by dissolving within minute in oral cavity after the contact with saliva without chewing and no need of water for administration. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa. FDOFs are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhea, sudden episode of allergic attacks, or coughing for those who have an active life style. It is also useful whether local action desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething.

Structural Features of Oral Mucosa

Structure: The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the sub mucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium.

The turnover time for the buccal epithelium has been estimated at 5-6 days and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 µm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue and the gingivae measure at about 100-200 µm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosa of the gingiva and hard palate are keratinized similar to the epidermis which contains ceramides and acylceramides (neutral lipids) which have been associated with the barrier function. The mucosa of the soft palate, the sublingual and the buccal regions, however, are not keratinized which are relatively impermeable to water and only have small amounts of ceramide. They also contain small amounts of neutral but polar lipids.

Permeability: The oral mucosa in general is intermediate between that of the epidermis and intestinal mucosa in terms of permeability. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. There are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosa.

For the better absorption of APIs in oral region permeation enhancer play important role. So if we want to absorb the drug mostly in mouth as drug released from formulation then there is the need of permeation enhancer. Some example of permeation enhancer given;

1) Aprotinin
2) Lauryl Ether
3) Azone
4) Benzylkonium chloride
5) Cetylpyridinium chloride
6) Cyclodextrin
7) Dextran sulphate
8) Menthol
9) Sodium glycodeoxycholate
10) Sodium taurodeoxycholate

Composition of Oromucosal Region

Oromucosal Cells: Are made up of proteins and carbohydrates. It is adhesive in nature and acts as a lubricant, allowing cells to move relative to one another with less friction. The mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems. 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 salivary glands as part of saliva. Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands.

Another feature of the oral cavity is the presence of saliva (digestive secretion) produced by three pairs of salivary glands (parotid, submandibular and sublingual glands). Saliva is mostly water with 1% organic and inorganic materials. The digestive enzyme present in saliva is salivary amylase, which breaks down starch molecules to shorter chains of glucose molecules. Saliva is made from blood plasma and thus contains many of the chemicals that are found in plasma. The major determinant of the salivary composition is the flow rate which in turn depends upon three factors: the time of day, the type of stimulus and the degree of stimulation. The salivary pH ranges from 5.5 to 7. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water rich environment of the oral cavity. This clearly indicates that the drug release can be released very rapidly by using the Kollicoat IR in the formulation. More over the films have shown faster disintegration and is inacceptable range. Thus developed oral thin film (OTF) technology is expected to be applicable for different kind of drugs that can improve the quality of life, especially pediatric and geriatric

patients.

TYPES OF ORAL RAPID DISSOLVING DRUG DELIVERY SYSTEM

A) Oral disintegrating tablet

An orally disintegrating tablet or orodispersible tablet (ODT) is a drug dosage form available for a limited range of over-the-counter (OTC) and prescription medications. ODTs differ from traditional tablets in that they are designed to be dissolved on the tongue rather than swallowed whole. The ODT serves as an alternative dosage form for patients who experience dysphasia (difficulty in swallowing) or for where compliance is a known issue and therefore an easier dosage form to take ensures that medication is taken. Common among all age groups, dysphasia is observed in about 35% of the general population, as well as up to 60% of the elderly institutionalized population and 18-22% of all patients in long-term care facilities during the last decade, ODTs have become available in a variety of therapeutic markets, both OTC and by prescription. An additional reason to use ODTs is the convenience of a tablet that can be taken without water.

Criteria for Fast dissolving Drug Delivery System:

The tablets should:

1) Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.

2) Be compatible with taste masking.

3) Be portable without fragility concern.

4) Have a pleasant mouth feel. Leave minimum or no residue in the mouth after oral administration.

5) Exhibit low sensitive to environmental condition as temperature and humidity.

6) Allow the manufacture of the tablet using conventional processing and packaging

7) Equipments at low cost.

8) 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.

9) 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.

10) Rapid dissolution and absorption of the drug, which will produce quick onset of action.

11) Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased.

12) Pregastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.

13) Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.

Benefits of fast dissolving tablets

1) Administered without water, anywhere, any time.

2) Suitability for geriatric and pediatric patients, who experience difficulties in swallowing.

3) Beneficial in cases such as motion sickness, suede episodes of allergic attack or coughing, where an ultra rapid onset of action required.

4) An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.

5) Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed.

Limitations of Mouth Dissolving Tablets

1) The tablets usually have insufficient mechanical strength. Hence, careful handling is required.

2) The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

TECHNIQUES FOR PREPARING FAST DISSOLVING TABLETS

Many techniques have been reported for the formulation of Fast dissolving tablets or Orodispersible tablets.

1. Freeze drying / lyophilization
2. Tablet Moulding
3. Spray drying
4. Sublimation
5. Direct compression
6. Mass extrusion

1) Freeze-Drying or Lyophilization

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight and poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminum foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophillization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

2) Tablet Molding:

Molding process is of two type's i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and posses a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30○C under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophillization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.

3) Spray Drying:

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or crosscarmellose or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking

agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate & croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g.sodiumbicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

4) Sublimation:

To generate a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane; benzene can be used as pore forming agents.

5) Direct Compression:

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of ODT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

(a) Superdisintegrants:

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The

presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

(b) Sugar Based Excipients:

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouth feel.

6) **Mass-Extrusion:**

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

EVALUATION TEST FOR FAST DISSOLVING TABLETS

1) Friability

The pharmacopoeial limit of friability test for a tablet is not more than 1% using tablet friability apparatus, carried out at 25 rpm for 4 min (100 rotations. This test is again not applicable for lyophilized and flash dose tablets, but is always recommended for tablets prepared by direct compression and molding techniques to ensure that they have enough mechanical strength to withstand the abrasion during shipping and shelf life.

2) **Moisture Uptake Study**

Fast dissolving tablets s usually contains high concentration of hydrophilic excipients with the minimum possible hardness which together contributes to their increased susceptibility to moisture uptake. In order to maintain their physical integrity and surface texture, special attention is required during the storage and packaging of these dosage forms. Therefore, moisture uptake studies are strongly recommended for this type of tablets. The test can be carried out by keeping ten tablets along with calcium chloride in a desiccators maintained at 37 °C for 24 hrs to ensure complete drying of the tablets. The tablets are then weighed and exposed to 75% RH, at room temperature for 2 weeks. The required humidity can be achieved by keeping saturated sodium chloride solution in the desiccators for 24 hrs. The tablets are reweighed and the percentage increase in weight is recorded.

3) Measurement of tablet porosity

The mercury penetration porosimeter can be used to measure the tablet porosity which is a relative assessment of the degree of water penetration in the formulation, responsible for its fast disintegration. This instrument is based on the capillary rise phenomenon wherein an excess pressure is required to cause a non-wetting liquid to climb up a narrow capillary. The pressure difference across the interface is given by the Washburn equation II, where the pressure drop is inversely related to the pore size. Pore sizes in the range of 0.06–360 μm, can be efficiently measured by this technique.

4) **Wetting Time and Water Absorption Ratio**

A study on wetting time and water absorption ratio reported the use of a piece of double folded tissue paper placed in a petridish containing 6 ml of water. One tablet was placed on this paper and the time for complete wetting of tablet was noted as wetting time. The wetted tablet was then weighed and the water absorption ratio, R, was determined according to equation

Eq. $R = 100 (Wa-Wb)/Wb$

Where Wb and Wa are the weights of tablet before and after water absorption, respectively.

5) **Friability**

The pharmacopoeial limit of friability test for a tablet is not more than 1% using tablet friability apparatus, carried out at 25 rpm for 4 min (100 rotations). However, it becomes a great challenge for a formulator to achieve friability within this limit for FDT product keeping hardness at its lowest possible level in order to achieve a minimum possible disintegration time.

6) Dissolution test

The development of dissolution methods for ODTs is comparable with the approach taken for conventional tablets and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent ODT. Other media such as 0.1N HCl and buffers (pH - 4.5 and 6.8) should be evaluated for ODT much in the same way as conventional tablets.USP dissolution apparatus 1 and 2 can be used.

FAST DISSOLVING FILMS

Mouth dissolving films offers an elegant route for systemic drug delivery. The improved systemic bioavailability results from bypassing first pass effect and better permeability due to a well supplied vascular and lymphatic drainage. Also, large surface area of absorption, easy ingestion & swallowing, pain avoidance makes the oral mucosa a very attractive and selective site for systemic drug delivery.

Fast dissolving films (FDF), a type of oral drug efficacy of Active pharmaceutical ingredient (API) delivery system for the oral delivery of the drug, was dissolving in the short duration oral cavity after the developed based on the technology of the transdermal contact with less amount of saliva as compared to patch. This delivery system consists of a thin film, which dissolving tablet which is simply placed on the patient's tongue or mucosal tissue, instantly wet by saliva; the film rapidly dissolves**.** Then it rapidly disintegrates and dissolves to release the medication for oralmucosal absorption. This fast dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the moist oral environment.

Fast dissolving films are most advanced form of solid dosage form due to its flexibility. It improves efficacy of active pharmaceutical ingredient dissolving in the short duration oral cavity after the contact with less amount of saliva as compared to dissolving tablet.

Special feature:

1) Available in various size and shape
2) Thin elegant film
3) Un-obstructive
4) Fast disintegration or dissolution
5) Rapid release

Advantages

1) No risk of chocking
2) Convenient dosing or accurate dosing
3) No need of water to swallow or chew
4) Small size for improved patient compliance
5) Rapid onset of actions
6) Ease of handling and transportation
7) Improved bioavailability for certain therapeutic ingredient.
8) Enhanced stability
9) Taste masking

Disadvantages:

1) It is hygroscopic in nature so it must be kept in dry places.
2) It also shows the fragile, granule property.
3) They require special packaging for the products stability and safety
4) High dose cannot be incorporated into the oral film.

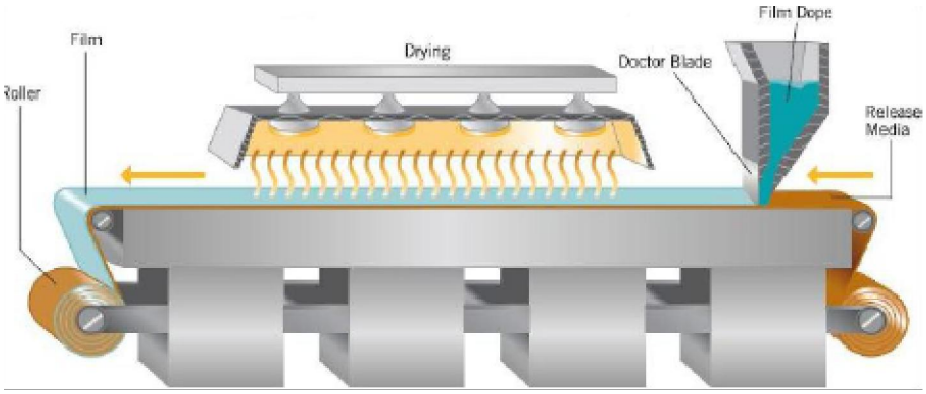
METHODS OF PREPARATION

One or more of the following process can be used to manufacture the mouth dissolving films:

1) Solvent casting
2) Semisolid casting
3) Hot melt extrusion
4) Solid dispersion extrusion
5) Rolling methods

1) Solvent casting method:

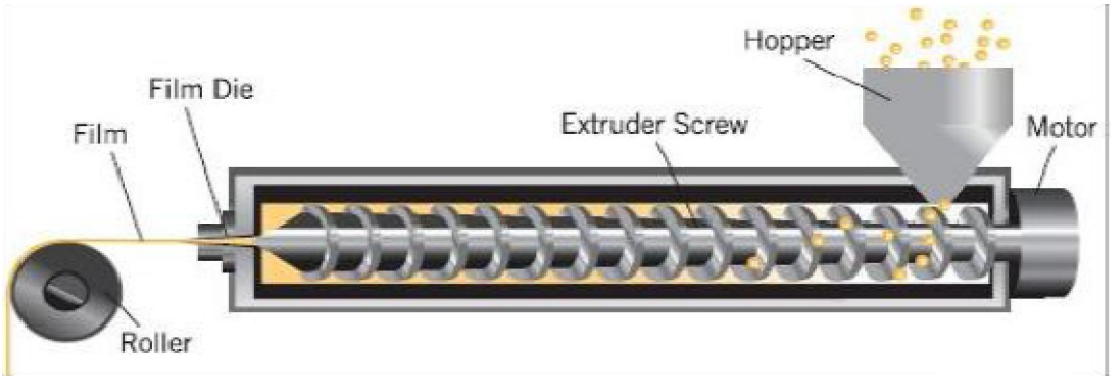
In solvent casting method excipients are dissolved in water, then water soluble polymers added in it and lastly drug is added and mixture is stirred to form homogeneous solution. Finally solution is casted in to the Petri plate and dried.



2) Semisolid Casting:

In this method, solution of water soluble film forming polymer is mixed to solution of acid insoluble polymer to form homogenous viscous solution (e.g. cellulose acetate phthalate and cellulose acetate butyrate). After sonication, it is coated on non-treated casting film. On drying the thickness of the film should be about 0.015-0.05 inches.. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

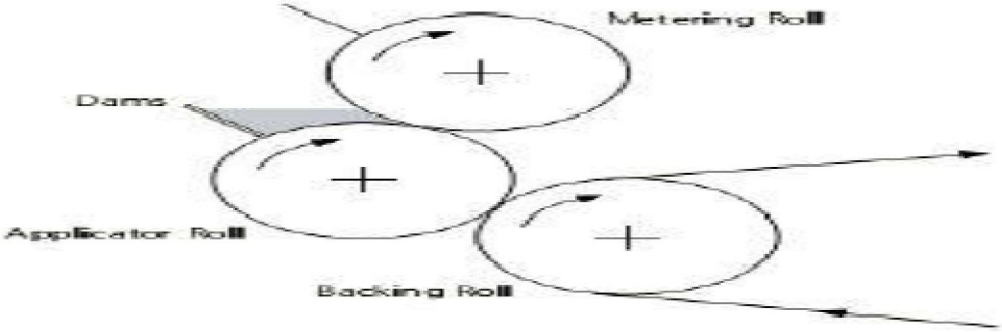
3) Hot Melt Extrusion:



In hot melt extrusion method, firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture and finally the melt is shaped in to films by the dies. There are certain benefits of hot melt extrusion which includes-

- Fewer operation units
- Better content uniformity
- An anhydrous processing

4) 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. Other ingredients including active agent are dissolved in small portion of aqueous solvent using high shear processor. Water soluble hydrocolloids dissolved in water to form homogenous viscous solution.

EVALUATION

1) Thickness:

As the thickness of film is directly concern with drug content uniformity, 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.

2) Morphological study

The morphological study of oral film is done by scanning electron microscopy (SEM) at a definite magnification. Study refers the difference between upper and lower side of the film. It also helps in the determination of the distribution of API.

3) 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.

Tensile strength=Load at breakage/Strip thickness x strip width.

4) 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.

5) Folding endurance:

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value.

6) Disintegration time:

Disintegration of orally fast dissolving films requires U.S.P. disintegration apparatus. The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in C.D.E.R. guidance can be applied to fast dissolving oral strips. Disintegration time will vary depending on the formulation but typically the disintegration range from 5 to 30 seconds. Although, no official guidance is available for oral fast disintegrating films.

7) In vitro drug release:

Dissolution studies of films are performed by U.S.P. XXIII type II apparatus in 6.8 phosphate buffer (500ml) and 0.1N HCl (500ml). The temperature required is 37±0.5°C and the rotation speed should generally 50 rpm. The samples are needed to withdrawn at various time intervals and should analyze spectrophotometrically.

Conclusion

The oral route is the most popular route for the administration of therapeutic agents by fast dissolving dosage forms because of the low cost of therapy and ease of administration which lead to increase in patient compliance. Extensive work was carried out till date in order to evaluate the fast dissolving tablets and among them; many are proved to have significant discriminatory power. The mouth dissolving films gained popularity because of low cost of therapy and ease of administration especially in geriatric and pediatric patients. They have the greater stability of a solid dosage form and good applicability of a liquid. More importantly, mouth dissolving films are travel friendly dosage form where water may not be carried out by person or patient. A new tablet dosage format, the fast dissolving tablets have been developed which offers the combined advantages of ease of dosing and convenience dosing in the absence of water or fluid. This type of dosage form has evolved as consumer friendly dosage form due to its attractive form as well as easy to use.

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