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Review Article

Fast dissolving drug delivery system: A novel approach

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Abstract

Recently Fast dissolving oral drug delivery systems are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improve the efficacy of active pharmaceutical ingredients by dissolving within minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration. Traditional tablets and capsules administered with an 8-oz. glass of water may be inconvenient or impractical for some patients. For example, a very elderly patient may not be able to swallow a daily dose of antidepressant. An eight year- old with allergies could use a more convenient dosage form than antihistaminic syrup. A schizophrenic patient in the institutional setting can hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic. For these complications the new approach may be convenient for patients.

Keywords: Fast dissolving tablets (FDT), Formulation, Excipient.

Introduction

A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves in the oral cavity without the need of water or chewing. Most fast-dissolving delivery system films must include substances to mask the taste of the active ingredient. This Masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients. These are also called melt-in-mouth tablets, porous tablets, orodispersible, quick dissolving or rapid disintegrating tablet.[1-2] The oral route of drug administration is the most important method of

administration of drug for systemic effect, despite of tremendous advancement in drug delivery system. Its ease of administration, pain avoidance and various advantages over other routes is the reason that the oral route achieved such popularity. But the most evident drawback of oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patient's incompliance particularly in case of pediatric and geriatric, bedridden, nauseous patients. A renewed interest has been addressed to oral solid dosage forms designed for prompt availability of therapeutic dose. Mouth dissolve products (tablets and films) may show greater patient acceptability and convenience. Fast-dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking of water or chewing. After disintegrating in mouth, enhanced the clinical effect of drug through pre-gastric absorption from mouth pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. More recently, Fast-dissolving buccal film drug delivery systems have rapidly gained acceptance as an important new way of administering drugs. They are usually used for pharmaceutical and nutraceutical products. It is the newest frontier in drug delivery technology that provides a very convenient means of taking medications and supplements. FDFs are also applicable when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores, or teething. Fast dissolving film is prepared using hydrophilic polymers that rapidly dissolve/disintegrate in the mouth within few seconds without water and eliminates the fear of chocking as an alternative to fast dissolving tablets. Basically the fast dissolving film can be considered as an ultra thin strip of postage stamp size with an active pharmaceutical ingredient and other excipients. Most fast dissolving films are having taste masked active ingredients. These masked active ingredients are swallowed by the saliva of patients along with the soluble and insoluble excipients.

The advantages of convenience of dosing and portability of mouth dissolving film have led to wider acceptability of this dosage form by pediatric as well as geriatric population equally. Because of fast dissolving behavior and fast adherence to the mucosa, fast dissolving films cannot be spit after application on to the tongue. They also impart unique product differentiation, thus enabling use as line extensions for existing commercial products. This novel drug delivery system can also be beneficial for meeting the current needs of the industry are improved solubility/stability, biological half life and bioavailability enhancement of drugs.

Formulation of fast dissolving film involves the application of both aesthetic and performance characteristics such as strip-forming polymers, plasticizers, active pharmaceutical ingredient, sweetening agents, saliva stimulating agent, flavoring agents, coloring agents, stabilizing and thickening agents. From the regulatory perspectives, all excipients used in the formulation of oral drug strips should be approved for use in oral pharmaceutical dosage forms. Fast dissolving films evolved over the past few years from the confection and oral care market in the form by consumers for delivering vitamins and personal care products.

Technology catalysts forecasts the market for drug products in oral thin film formulations to be valued at $500 million in 2007 and can reach $2 billion in near future according to technology catalysts.[3]

Ideal properties of fast dissolving tablets

Some ideal properties of this type of tablet is,

a) Not require water or other liquid to swallow[4].

b) Easily dissolve or disintegrate in saliva within a few seconds.

c) Have a pleasing taste.

d) Leave negligible or no residue in the mouth when administered. [5]

e) Be portable and easy to transport.

f) Be able to be manufactured in a simple conventional manner within low cost.

g) Be less sensitive to environmental conditions like temperature, humidity etc. [5, 6]

Advantages of fast dissolving tablets

FDT can be administer to the patients who cannot swallow tablets/cap., such as the elderly, stroke victims, bedridden patients, & patients who refuse to swallow Such as pediatric, geriatric & psychiatric patients. Rapid drug therapy is possible. Certain studies concluded

increased bioavailability/proved rapid absorption of drugs through pregastric absorption of drugs from mouth, pharynx & esophagus as saliva passes down.[7, 8] Some advantages of the recent oral fast dissolving drug delivery system are depicted in the figure1 given below:

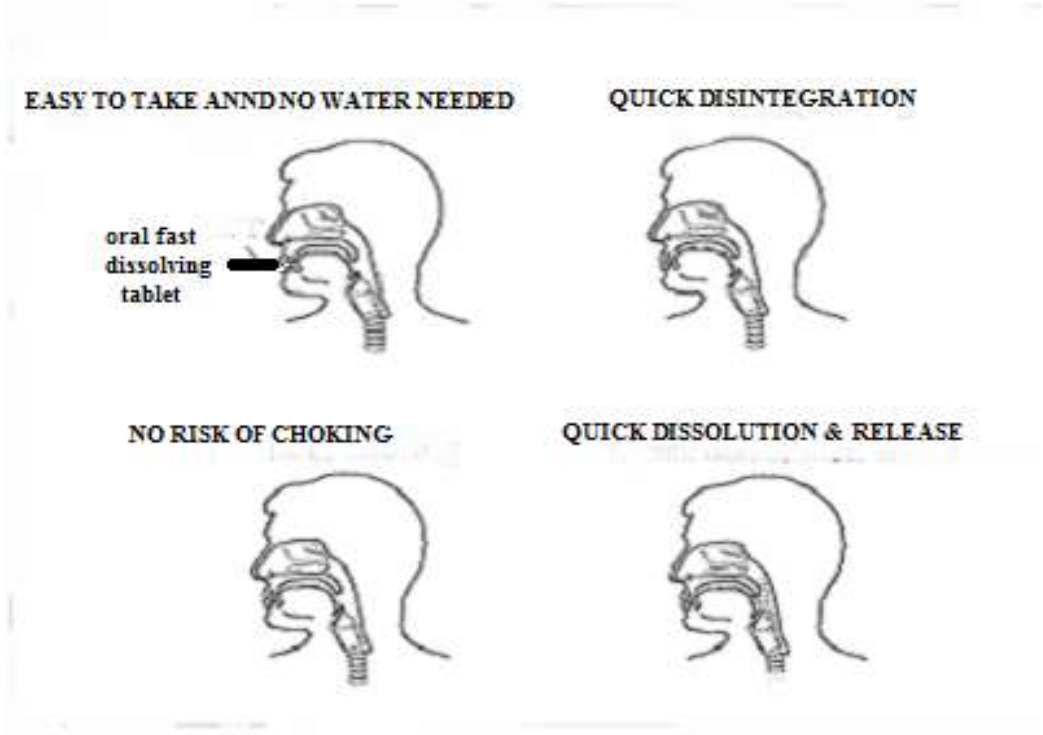


Figure 1: Advantages of Oral Fast Dissolving Tablets

Table 1: Examples of some Drug used in fast dissolving drug delivery system.

Sl No	Types of Drug	Examples
1	Analgesic and anti-inflammatory Agents	Ibuprofen, Proxicam, MefenamicAcid
2	Anti-bacterial Agent	Erythromycin, Tetracycline, Doxycycline,Rifampcin
3	Anti-fungal Agents	Griseofulvin,Miconazole
4	Anti-Malarials	Chlorquine, Amodiaquine
5	Anti-Gout Agent	Allopurinol, Probenecid
6	Anti-Hypertensive	Amlodipine, Nefidipine
7	Anti-Coagulants	Glipizide,Tolbutamide
8	Anti-Protozoal Agents	Benznidazole, Tinidazole
9	Anti-Thyroid agent	Carbimazole
10	Cardiac Inotropic Agent	Digitoxin
11	Gastro-Intestinal Agents	Omeprazole, Ranitidine, Fomatidine
12	Nutritional Agents	Vitamin A,Viitamin B, Vitamin D, etc.
13	Oral Vaccine	Influenza, Hepatitis,Polio, Tuberculosis,etcs

Composition of the fast dissolving tablets

Fast dissolving film is a thin film with an area of 2-8 cm^2 containing an active ingredient. The immediate dissolution, in water or saliva is reached through a special matrix from water-soluble polymers. Drugs can be incorporated up to a single dose of 30mg**.** Formulation considerations have been reported as important factors affecting mechanical properties of the films. From the regulatory perspectives, all excipients used in the formulation should be generally regarded as safe (i.e. GRAS-listed).

Table 2: A typical composition of fast dissolving tablets.

Sl No	Types of ingredients	Percentage in formulation
1	Active pharmaceutical agent	1-25 %
2	Water soluble film forming polymer	40-50 %
3	Plasticizer	0-20 %
4	Sweetening agent	3-6 %
5	Saliva stimulating agent	2-6 %
6	Colors and Flavors	0-10 %

Formulation of fast dissolving tablets

The ideal characteristics of a drug to be selected: No bitter taste, Dose lowers than 20mg.,Small to moderate molecular weight, Good stability in water and saliva, Partially none ionized at the oral cavities pH, Ability to diffuse and partition into the epithelium of the upper GIT, Ability to permeate oral mucosal tissue. [9, 10]

Superdisintegrants

Crosspovidone, Microcrystalline cellulose, sodium starch glycollate, Sodium carboxy methyl cellulose, pregelatinzed starch, calcium carboxy methyl cellulose, and modified corn starch. Sodium starch glycollate has good flowability than crosscarmellose sodium. Cross povidone is fibrous nature and highly compactable.

Flavors

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, 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. The amount of flavor needed to mask the taste depends on the flavor type and its strength. Peppermint flavour, cooling flavor, flavor oils and flavoring aromatic oil, peppermint oil, clove oil, bay oil, anise oil, eucalyptos oil thyme oil, oil of bitter almonds. Flavoring agnets include vanilla, citus oils, and fruit essences.

Fillers

Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulfate, pregelatinized starch, magnesium trisilicate, aluminium hydroxide.

Surfaceactive agents

sodiumdoecylsulfate, sodiumlaurylsulfate, polyoxyethylene sorbitan fatty acid esters (Tweens), sorbitan fatty acid esters (Spans), polyoxyethylene stearates .

Lubircants

Stearic acid, Magnesium stearate, Zinc state, calcium state, talc, polyethylene glycol, liquid paraffin, magnesium laury sulfate, colloidal silicon dioxide.

Binder

Hydroxypropy lmethylcellulose.

Color

A full range of colors is available including FD& C colors, EU colors, natural coloring agents, and natural juice concentrates, pigments such as titanium oxide, silicon dioxide and zinc dioxide and custom pantone-matched colors. These all coloring agents should not exceed Concentration levels of 1% w/w. these agents are incorporated when some of the formulation ingredients or drugs are present in insoluble or suspension form. Sunset yellow, Amaranth is also used.

Film forming polymer

A variety of polymers are available for preparation of fast dissolving films. The polymers can be used alone or in combination to improve hydrophilicity, flexibility, 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. The film obtained should be tough enough so that there won't be any damage while handling or during transportation. The robustness of the strip depends on the type of polymer and the amount in the formulation. The various polymers which can be used for making fast dissolving films must be water soluble with low molecular weight and excellent film forming capacity, since the primary use of all thin film oral dosage forms relies on their disintegration in the saliva of the oral cavity. The polymer employed should be non-toxic, non-irritant with good wetting and spreadability property. The polymer should not be very expensive and should be readily available. Water soluble polymer that may be used include natural gums such as xanthan, guar, acacia, tragacanth other available polymers include cellulose or cellulose derivatives, hydroxypropylmethyl cellulose with different grades like HPMC E15, HPMC E5, HPMC K4M, HPMC K100, hydroxyethylcellulose, hydroxypropylcelluose, carboxymethylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, pullulan, gelatin. Modified starches are also used for preparation. The physicochemical characteristic of the polymer or polymers selected for film formulation play a vital role in determining the resultant disintegration time of the cast thin film oral dosage form.

Saliva stimulating agents

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in faster disintegration of the fast dissolving film. These agents can be used either alone or in combination. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. Commonly used saliva stimulating agents are citric acid, lactic acid, ascorbic acid, malic acid, tartaric acid.

Preparation of fast dissolving tablet formulation

Freeze –Drying method

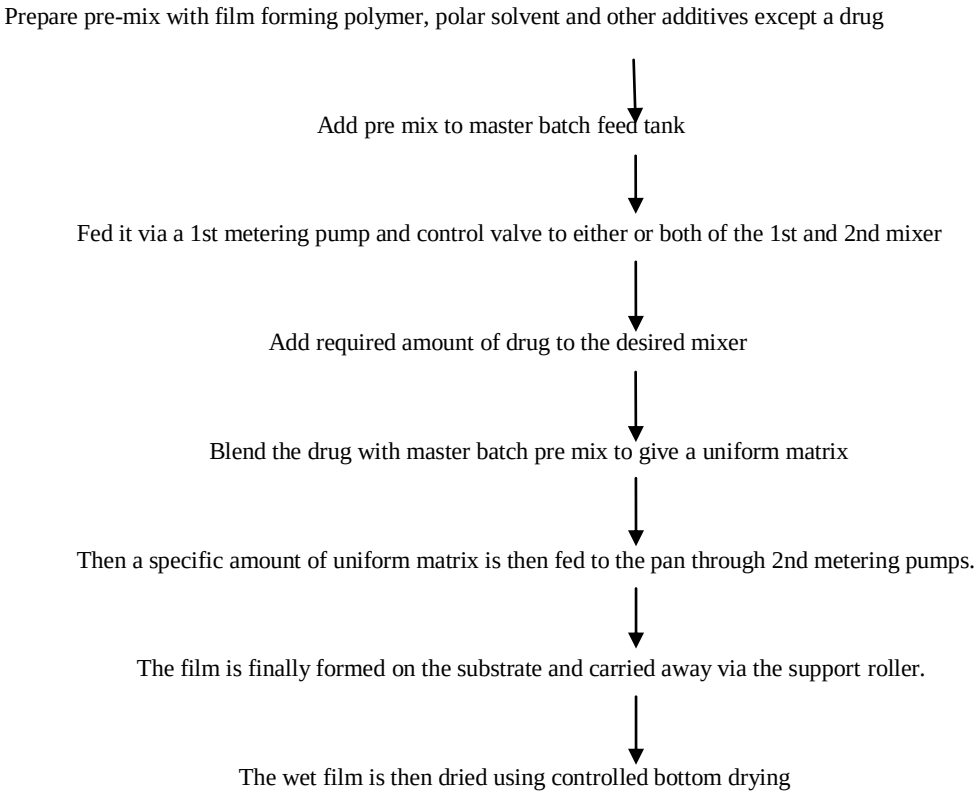
Freeze-drying allows immediate dissolution of the tablets because of their high porosity, and enhances drug stability, especially for moisture-sensitive substances; on the other hand, a porous network is associated with low physical resistance and high friability. Special packaging is required in some cases.

Sublimation Technique

In this method a subliming material like camphor, is removed by sublimation from compressed tablets and high porosity is achieved due to the formation of many pores where camphor particles previously existed in the compressed tablets prior to sublimation of the camphor. A high porosity was achieved due to the formation of many pores where camphor particles previously existed in the compressed mannitol tablets prior to sublimation of the camphor. These compressed tablets which have high porosity (approximately 25-30%) rapidly dissolved within 12 to15 seconds in saliva. Granules containing nimusulide, camphor, crospovidone, and lactose were prepared by wet granulation technique. Camphor was sublimed from the dried granules by vacuum exposure Conventional methods like dry granulation, wet granulation and direct compression with highly soluble excipients, super disintegrates and/or effervescent systems can also be used.

Rolling method

In this method the film is prepared by preparation of a pre-mix, addition of an active and subsequent formation of a film. The flowchart of the rolling method for the preparation of the fast dissolving tablets has been given below.



Semisolid casting method

This method is preferably adopted when acid insoluble polymers are to be used in the preparation of the films. 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. The flowchart has been given below.

Solution of water soluble film forming polymer is prepared

↓

Resulting solution is added to a solution of acid insoluble polymer

↓

Appropriate amount of plasticizer is added so that gels mass is obtained

↓

Finally the gel mass is casted in to the films or ribbons using heat controlled drums.

Solid dispersion extrusion method

The term solid dispersions refer to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers.

Drug is dissolved in a suitable liquid solvent

↓

Then solution is incorporated into melt of polyethylene glycol, obtainable below 70°C

↓

Finally the solid dispersions are shaped into the films by means of dies

Solvent casting method

Fast dissolving films are preferably formulated using the solvent casting method, whereby the water soluble ingredients are dissolved to form a clear viscous solution 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. The flowchart has been given below.

Packaging of the fast dissolving tablets

A variety of packaging options are available for fast dissolving films. In the pharmaceutical industry it is vital that the package selected adequately preserve the integrity of the product. Single packaging is mandatory for films, which are pharmaceutical products; an aluminum pouch is the most commonly used. Applied Pharma Research (Switzerland)-Labtec GmbH of Germany has developed the Rapid Card, a proprietary and patented packaging system which is specifically designed for the mouth dissolving films. The Rapid Card is exactly the same size as a credit card and holds three mouth dissolving films on each side. Every dose can be taken out individually, allowing the patient to carry six single, packaged doses of his medication in his purse or wallet and have it readily available. [11]

The material selected must have the following characteristics:

1. They must protect the preparation from environment conditions.
2. They must be FDA approved.

3. They must be non-toxic.
4. They must not be reactive with the product.
5. They must not impart to product tasted or odors.
6. They must meet applicable tamper-resistant requirement

Water soluble ingredients are dissolved in water and API and other agents are dissolved in suitable

Solvent to form a clear viscous solution

↓

Both the solutions are mixed

↓

Degassed under vacuum

↓

Resulting solution is cast as a film

↓

Film is dried in drying oven and collected

Mechanism of the fast dissolving tablets

The mechanism of the fast dissolving drug delivery system can be best described by the figure 2 given below;

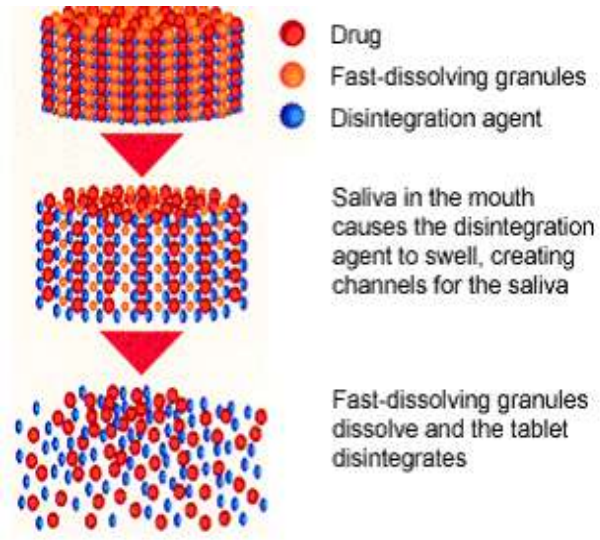


Figure 2: Mechanism of the fast dissolving tablets

Foil, paper or plastic pouches

The flexible pouch is a packaging concept capable of providing not only a package that is temper-resistance, but also by the proper selection of material, a package with a high degree of environmental protection. A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling, or sealing equipment. The pouches can be single pouches or aluminum pouches.

Single pouch and aluminum pouch

Soluble film drug delivery pouch is a peel able pouch for "quick dissolve" soluble films with high barrier properties.

The pouch is transparent for product display. Using a 2 structure combination allows for one side to be clear and the other to use a cost-effective foil lamination. The foil lamination has essentially zero transmission of both gas and moisture. The package provides a flexible thin film alternative for nutraceutical and pharmaceutical applications. The single dose pouch provides both product and dosage protection. Aluminum pouch is the most commonly used pouch.

Blister card with multiple units

It consists of two components: the blister, which is the formed cavity that holds the product, and the lid stock, which is the material that seals to the blister. The material used to form the cavity is typically a plastic, which can be designed to protect the dosage form from moisture. [12]

Evaluation tests of fast dissolving tablets [13]

Angle of Repose:

$$Tan(q) = h/r$$

Therefore $q = \tan^{-1}(h/r)$

Where q = Angle of repose h = height of the cone r= Radius of the cone base

Porosity:

The porosity € of powder is defined as the ratio of void volume to the bulk volume of the packaging.

$$€= V_b - V_p/ V_p = 1- V_p/V_b$$

Porosity is frequently expressed in percentage and is given as $\% € = (1 - V_p/ V_b) \times 100$.

Compressibility:

It is an important measure obtained from bulk density and is defined as, P_b=before compressed volume, P_u=after compressed volumes

$$C=P_b-P_u/P_b \times 100$$

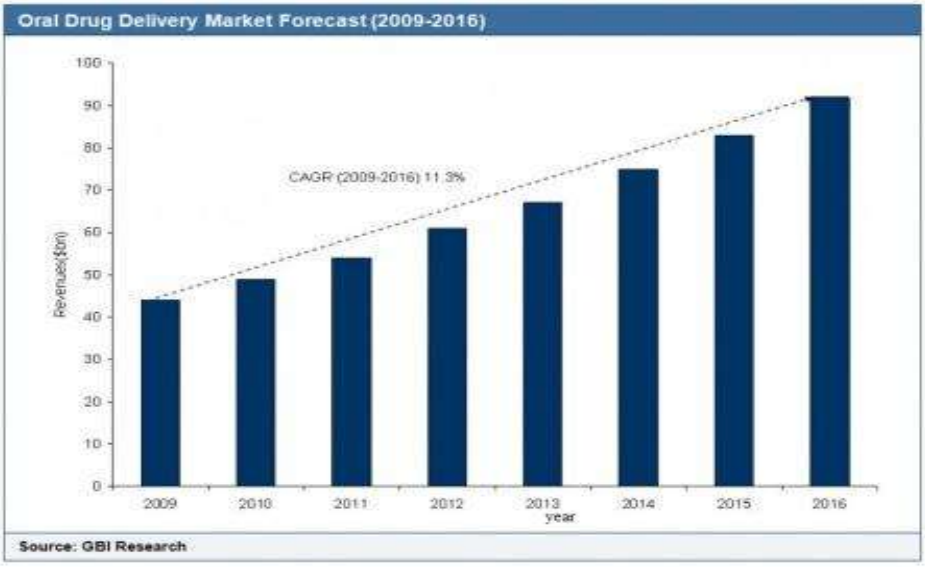


Figure 3: Oral Drug delivery system market forecast (2009-2016)

Conclusion

With continued innovations in pharmaceutical excipients, one can expect the emergence of more novel technologies for Fast Dissolving Tablets in the days to come. These innovations may involve modifying formulation composition and processing to achieve new performance end-points or the merger of new technological advances with traditional pharmaceutical processing techniques for the production of novel Fast dissolving dosage forms. The Fast dissolving drug delivery system have potential advantages over conventional oral dosage forms with their improved

patient compliance; convenience, bioavailability and rapid onset of action which drawn the attention of many manufactures over a decade. This formulations obtained by some of these technologies have sufficient mechanical strength, quick disintegration/dissolution in the mouth. Many drugs can be incorporated in this type of formulation especially unpalatable drugs. The research is still going on. More products need to be commercialized to use this technology properly. Thus such a delivery system may be developed for most of the available drugs in near future. It is reasonable to expect that future trends in innovations of drug delivery systems will continue to bring together different technological disciplines to create novel technologies.

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