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Research Article

Fast dissolving tablets - An overview

Dinesh Kumar Pandurangan*[1], Tejaswi Vuyyuru[1], Dhatrija Kollipara[2]

[1]Department of Biotechnology, Acharya Nagarjuna University, Guntur – 522 510, India
[2]Department of Pharmaceutics, Rahul Institute of Pharmaceutical Science & Research, Chirala-523157, Andhra Pradesh, India

ABSTRACT

Despite disadvantage, oral drug delivery remains the preferred route of drug delivery. Oral fast dissolving tablets have received important acceptance as novel drug delivery system for treatment of various diseases upon introduction in the mouth disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. This article provides comprehensive review of fast dissolving tablets.

Keywords: Fast dissolving tablets; Drug delivery system; Ideal characteristics; Manufacturing technology

INTRODUCTION

Drug delivery systems are strategic tool for expanding markets, extending product life cycle. Oral routes of drug administration have a wide acceptance up to 50-60% of total dosage forms. It is most popular route for systemic effects due to ease of ingestion, pain, versatility, less patient compliance. The demand for solid dosage forms can be dissolved & suspended in water, chewed or rapidly dissolved in mouth. The dosage forms are placed in mouth, allowed to dissolve in saliva and swallowed in normal way. Most fast dissolving tablets include substances to mask bitter taste of active ingredient. Faster the dissolution, quick absorption [only in ionized form of drug] and quick on set of action. Fast dissolving tablets are also known as mouth dissolving tablets, melt-in mouth dissolving tablets, oro dispersible tablets, rap melts, porous tablets, quick dissolving tablet. Fast dissolving tablets dissolve or disintegrate in oral cavity without need of water. Some tablets are designed in saliva within a few seconds, and so called 'true fast dissolving' tablets. (Seeger H et al, 1998).

Fast dissolving tablet can be defined as solid dosage form that can disintegrate into smaller granules which slowly dissolve in mouth. A fast disintegrating or dissolving system or tablet can be defined as a solid dosage form that can disintegrate or dissolve within 30 seconds in the oral cavity resulting in a solution or suspension without administration of water. Oro dispersible tablet has to be placed in oral cavity where it disperses rapidly before swallowing. Zydis, is best known fast dissolving tablet preparation. It is produced by lyophilizing of the drug in a matrix consisting of gelatin. Glibenclamide a second generation anti diabetic drug to develop fast dissolving tablet using crospovidone [CP], as super disintegrating agent. Glibenclamide [GLB] is a sulphonyl urea derivative used for treatment of diabetes mellitus -2. It is insoluble in water and poor gastrointestinal absorption and bio availability.

* Corresponding Author
Email: dineshclbaid@gmail. com
Contact: +91-9966639425
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Pharmacokinetics

It deals with absorption, distribution, metabolism, excretion. After absorption drug attains therapeutic level and elicit pharmacological effect. so both rate and extent of absorption is important. In conventional dosage form there is delay in disintegration and dissolution. But in case of fast dissolving tablets rapidly disintegration in oral cavity and dissolution is fast. The faster dissolution of tablet takes place in mouth absorption from mouth, pharynx, and esophagus. Some factors like age, sex, pH, blood flow through gastrointestinal taken into consideration because elders may be considered as separate unique medical care preparation. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue, disease state drug interaction. In geriatric patients, decrease in body mass and total body water result in decreased volume of distribution of lipid soluble drugs. Duration and intensity of action depends upon rate of drug removal from body i. e. biotransformation. Decrease in renal volume, regional blood flow to liver reduces bio transformation of drug through oxidation, reduction, and hydrolysis. Excretion by renal clearance is slowed, thus half life of renal excreted drugs increase. The metabolism of fast dissolving tablets is very easy and can be obtained very faster. Drinking water plays an important role in swallowing of oral dosage forms. (Verily P et al, 1989).

Pharmacodynamics

Drug reception interaction impaired in elderly as well as in young adult due to undue development of organ.

Decreased ability of body to respond baro reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking anti hypertensive like prazosin.

Decreased sensitivity of CVS to beta adrenergic agonist and antagonist

Immunity is less and taken into consideration while administered antibiotics.

Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates.

Concomitant illness is often present in elderly, which is also taken into consideration while multiple drug therapy prescribed.

Research workers have clinically evaluated drug combination for various classes' cardiovascular agents, diuretics, anti-hypertensive in geriatrics. The combination choice depends on disease state of the patient. (Verily P et al, 1989)

Difficulties with existing oral dosage form

Patients may suffer from tremors therefore they have difficulties to take powder and liquids. In dysphasia physical obstacles and adherence to an esophagus may cause gastrointestinal ulceration.

Swallowing of solid dosage forms like tablet and capsules

Produce difficulty for young adult and incomplete development of muscular and nervous system and elderly patients suffer from dysphasia.

Liquid medicaments [suspensions and emulsion] are packed in multidose container; therefore achievement of uniformity in the content of each dose may be difficult.

Buccal and sublingual formation may cause irritation to oral mucosa, so patients refused to use such medications.

Cost of products is main factor as parenteral formulations are most costly and discomfort. (Mallet L et al, 1996)

Advantages of fast dissolving tablets

Ability to provide advantages of liquid medication in the form of solid preparation

- Improved compliance/added convenience
- Better taste
- No chewing needed
- Allows high drug loading
- Improved stability
- Suitable for controlled as well as fast release actives
- Cost-effective (Hanawa T et al, 1995)

Idea characteristics of fast dissolving delivery system

- It allows high drug loading.
- Improved patient compliance.
- Leave little or no residue in mouth after oral administration.
- Pleasant mouth feels properties, adequate hardness.
- Should have adequate taste masking properties.
- No need of water for oral administration. (Carrabolla J et al, 1997)

Mechanism of fast dissolving tablets

To achieve the tablets fast dissolving properties

Water must quickly enter into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet.

Incorporation of an appropriate disintegration agent or highly water soluble excipients in the tablet formulation

These are some under mentioned mechanisms by which the tablet is broken suspension of drug.

The mechanisms are

- High swell ability of disintegrates
- Chemical reaction.
- Capillary action. (Francesco C et al, 2005)

Conventional technique used in the preparation of fast dissolving tablets

- Freeze drying technique
- Tablet molding technique
- Spray drying technique
- Direct compression technique
- Sublimation technique
- Mass extrusion technique

Freeze drying technique (Zydis Technology)

Lyophilization can be used to prepare tablets that have very porous open matrix network into which saliva rapidly moves to disintegrate lyophilized mass after it placed in mouth. The drug is entrapped in a water soluble matrix which is freeze dried to produce a unit which rapidly disperses when placed in a mouth. A part from matrix and active ingredients the final formulation may contain other excipients, which improve the

Table 1: Drugs used in fast dissolving delivery system

S. No	Therapeutic activity	Drugs used
1.	Analgesic and anti- flammatory agents	Aloxiprin, fenbufen, meclofenamic acid, oxaprozin, oxyphenbutazone, ibuprofen, nabumetone, piroxicam
2.	antihelmentics	Albendazole, cambendazole, ivermectin, pyrantel, praziquantel, mebendazole, thiabendazole, hydroxyl naphthoate
3.	Anti –arrhythmic agents	Amiodarone hcl, disopyramide, flecainite acetate, vanidine sulphate,
4.	Anti-bacterial agents	Cinoxicam, clofazimine, cloxacillin, doxycycline, nitrofurantoin, ehionamide, banethamine, pencillin, sulphadoxine, sulphabenzamide, sulphapyridine, trimethoprim.
5.	Anti-**c**oagulants	Dicoumarol, dipyrimidine, phenindione, nicoumalone.
6.	anti-depressant	Amoxapine, ciclazindol, mianserinHCL, trazodoneHCL, trimipramine maleate, maprotilineHCL.
7.	ANTI-DIABETICS	acetohexamide, chlorpropamide, glibenclamide, gliclzide, glipizide, tolbutamide.
8.	Anti-epileptics	Clonazepam, methion, phenacemide, phenobarbetone, sulthiame, phenatoin**,** oxecarbazepine, methylphenobarbitone.
9.	Anti-fungal	Clotrimazole, flucytocin, grisiofulvin, natomycin, amphitercin, terconazole, tioconazole, itraconazole,
10.	Anti-malarial	Amodiaquine, chloroproguanil HCL, pyramethamine, chloroquine, mefloquine**,**
11.	Anti-muscarnic agents	Atropine, biperdine, hyoscyamine, oxyphencyclamine HCL, tropicamide
12.	Anti-protozoa agents	Clioquinol, benznidazole, diloxamidesfuroate, metronedazole, benznidazole, tinidazole.
13.	Anxiolytics, seditives, hypnotics and neuroleptics	Alprazolam, barbitone, bentazepam, bromazepam, clozapin, bromperidol, diazepam, ethinamate, flurazepam, droperidol.
14.	Cardiac inotropic agents	Amrinone, digitoxin, digoxin, medigoxin, enoximone.
15.	Anti-parkinsonian agents	Bromocriptine, mesylate, ysuride maleate.

process or quality of final product. these include suspending agents, wetting agents, preservatives, antioxidants, colors, flavors. The freeze drying can be preferred for formulations which are water soluble, low dose, chemically stable, small particles and tasteless.

Lyophilization is relatively expensive and time consumption and time consuming manufacturing process. Other drawbacks include fragility, which make the use of conventional packing difficult and poor solubility during storage under stressful condition. Corveleyn and Ramon investigated the influence of various formulation and process parameters on the characteristics of rapidly disintegrating tablets in lyophilized form using hydrochlorothiazide as a model drug. They have concluded that maltodxtrins are use full in formulation of fast dissolving tablets made by freeze drying.

Tablet molding

In this technique water soluble ingredients are used so that disintegrate and dissolve rapidly. The powder blend is moistened with a hydro alcoholic solvent and is molded in to a tablet using compression pressure lower than used in conventional tablets compression. The solvent is then removed by air-drying. Molded tablets have a porous structure that enhances dissolution. Two problems commonly encountered are mechanical strength and poor taste masking characteristics. Using binding agents such as sucrose, acacia, and polyvinyl pyrrolidine can increase the mechanical strength of the tablet. To overcome poor taste masking characteristic Van Scio incorporated drug containing discrete particles, which were formed by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium bicarbonate, lecithin, polyethylene glycol and active ingredient into a lactose based tablet triturate form.

Mass extrusion

This technology involves softening of active blend using the solvent mixture of water soluble polyethylene glycol and menthol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules for bitter drugs and their by achieve taste masking. (Habib W et al, 2000)

Patented technologies of FDTs

Currently four fast dissolving/disintegrating technologies have reached the US market:

- Orasolv (cyma labs, inc)
- Durasolv (cyma labs, inc)

Three others are available outside US:

- Flash dose (fizz technologies, ltd)
- Flash tab (prographarm group)

- Or quick (kV pharmaceutical co., inc.)

Zydis Technology

Zydis fast dissolve technology is a unique, freeze dried oral solid dosage form that disperse instantly in mouth no water required. Zydis technology can help to extend products life cycle. When Zydis units are put into a mouth, the freeze dried structure disintegrates instantaneously in mouth as little as 3 seconds. The Zydis matrix is composed of many materials designed to achieve a number of objectives. to impart strength and resilience during handling, polymers such as gelatin, dextrin alginates are incorporated. These form a glossy amorphous structure, which impart strength.

To obtain crystalline, elegance and hardness, saccharine such as mannitol or sorbital are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Zydis fast dissolve tablets are physically robust, packaged in a discreet blister pack and easily taken without water

Limitation

- The amount of drug could be incorporated should be less than 400mg for insoluble drugs and less than 60mg for soluble drugs
- The particle size of insoluble drugs should not be less than 50µm and not more than 200µm to prevent sedimentation during processing.

Advantages

- Buccal pharyngeal and gastric regions are all areas of absorption for this formulation. any pre –gastric absorption avoid first –pass metabolism and can be advantage in drugs that undergo a great deal of hepatic metabolism
- The zydis formulation self-preserving because the final water concentration in freeze dried product is too low to allow for microbial growth.

Disadvantages

- the process of freeze drying is the relatively expensive manufacturing process
- It has poor stability at higher temperature and humidity.
- The freeze drying is time consuming process.
- It has poor physical resistance.

Durasolv Technology

Durasolv is the patented technology of cima labs. The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring low amounts of active ingredients.

Advantages

Durasolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tabletting.

The Durasolv product is thus produced in a faster and in more effective manner

Disadvantages

It is not compatible with larger doses of active ingredients because the formulation is subjected to high pressures on compaction.

The drug powder coating May fractured during compaction, exposing the bitter tasting drug to patient's taste buds

Orasolv Technology

Orasolv technology has been developed by CIMA labs. IN This system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low comparison force in order to minimize oral dissolution type conventional blenders and tablet mention is used to produce tablets. The tablets produced are soft and friable and packaged in specially designed pick and place system.

Advantages

- The orosolv formulation are not hygroscopic
- The formulation can accommodate high doses
- It provides a distant, pleasant sensation of effervescence in the mouth

Disadvantages

- Poor mechanical strength
- A weaker and moor brittle tablet in comparasition with conventional tablets
- Manufacturing request a control environment at low relative humidity

Wowtab Technology

Wow tab technology is patented by yamanouchi pharmaceutical co. wow means without water. In this process, combination of low mould ability saccharides and high mould ability saccharides used to obtain a rapidly melting strong tablet. The active ingredient is 1mied with low mould ability saccharine and granulated with high mould ability saccharine and compressed into tablet.

Advantages

- Offer superior mouth feel due to smooth melt action.

- It is suitable for both conventional and blister packaging. (Habib W et al, 2000)

Oral vaccine

Vaccines designed to prevent or reduce the symptoms of diseases is a representative influenza, meningitis, hepatitis, whooping cough, polio, typhoid, AIDS, measles, Lyme disease, travelers atrophic rhinitis, foot and mouth disease, swine, pneumonia, and other infections and auto immune conditions affecting companion and farm animals. (Bogner RH et al, 2002)

Evaluation of tablets

All the formulated fast dissolving tablets were subjected to the following quality tests,

- Weight variation
- Friability
- Hardness
- Water absorption ratio
- Taste/mouth feel
- In vitro dissolution studies

Weight variation

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of tablets were also determined accurately and the weight variation was calculated.

Friability

It is determined by taking six tablets from each formulation with help of Roche Fribrilator. After that the pre weighed six tablets were rotated at 25rpm for 4 min. Then tablets were reweighed after removal of fine particles using 60 mesh and the percentage of weight loss is calculated.

$$\% \text{ friability} = [\text{loss in weight/initial weight}] \times 100$$

$$\%FRIABILITY = [(W1-W2) \times 100]/w1$$

Hardness

The hardness of tablet is an indication of its strength, measuring the force required to break the tablet across test it. The force is measured in kg and the hardness of tablet of about 3-5 kg/ cm^2 is satisfactory for uncoated tablets. Hardness of tablets was determined by Monsanto hardness tester.

Disintegration test

Disintegration time was measured in artificial saliva [pH5. 8] of 900ml. according to USP 24 method disc at 37±5C temperature. The disintegration time of individual tablets is recorded and from this the average weights are calculated and the time in sec recorded for complete disintegration of the tablet.

Water absorption ratio

A small piece of tissue paper folded twice was placed in a small Petri dish containing 6ml of water. A tablet was put on paper and time required for complete wetting was measured. the wetted tablet was then reweighed. Water absorption ratio can be determined by using formula

$$R=100\times Wa-Wb/Wb$$

Wb is the weight of tablet before water absorption

WA is the weight of tablet after water absorption. (Khan KA et al, 1975)

In vitro drug release studies

The gliclazide fast dissolving tablets were subjected to in vitro drug release studies in ph 6. 8 phosphate buffer for 30min to access the ability of the formulation for providing immediate drug delivery.

Drug release studies were carried out in 8 stage dissolution test apparatus (DISSO 2000, lab INDIA) using 900ml of dissolution medium (ph6. 8 phosphate buffer) maintained at 37±1ºc. the tablets were kept in the cylindrical basket and rotated at 100 rpm. 5ml of sample from dissolution medium were withdrawn at each interval (2, 3, 5, 10and 30min) and 5ml of fresh sample was replaced each time. The samples were filtered and from the filtrate 1ml was taken and diluted to 10mlwith ph 6. 8 phosphate buffer. The absorbance of samples was measured at max 227. 2 nm using UV spectrophotometer.

In vitro dissolution kinetics studies

The drug released data were plotted and tested with Zero order (cumulative % Drug released Vs time) first order (log %remained Vs time). The zero order release kinetics

First order release kinetics

Log q=log Q^o +K1t 2. 303

the in vitro dissolution kinetics parameters, dissolution rate constants (k), correlation coefficient, the times (t50) for drug released (half life) and dissolution efficiency were calculated and presented in the tables from the slopes of linear plots, the dissolution rates were calculated, the first order equation describes the release from systems where release rate is concentration dependent. Where Q_o is in the initial amount of the drug, t in min and k1 describes dissolution rate constant of first order kinetics. A plot of the logarithm of percent of drug remained against time will be linear. If the release obeys first order release kinetics. (Verily P et al, 1989)

Dissolution efficiency

DE is defined as the area under the dissolution curve. Up to the time‘t’ expressed as a percentage of area of

trapezoid described by 1oo% dissolution in the same time.

$$DE=y.\ DT$$

$$Y_{idd.\ t}$$

The index DE30 would relate to the dissolution of drug from a particular formulation after 30 min could only be compared with DE30 OF other formulations.

One way Anova

One way analysis of variance (ANOVA) compares the means of three or more groups. The null hypothesis is that all column means are equal, and p value testing this null hypothesis.

The one way ANOVA test assumes that data are randomly sampled from larger populations (or at least are representative of those populations) that each value was obtained independently of others, that the populations are scattered accordingly to a Gaussian distribution, and that the SD of the two populations are equal.

It shows the intermediate calculations that lead to calculate F value is less than tabulated value.

Two way Anova

When two independent factors might have effect on the response variable of interest, it is possible to design the test so that an analysis of variance can be used to test for effects of the two factors simultaneously. Such a test is called a two-factor analysis of variance. With this we can test sets of hypothesis with some data at the same time.

In this the data are classified according to two different criteria of factors. The procedure for analysis of variance is somewhat different than the one followed while dealing with problems of one way ANOVA (. statistical methods S. P. Gupta, 34th edn, 2005-pgno-1019).

Similarity and dissimilarity factor

Purpose of dissolution profile comparison

For accepting product sameness under SUPAC –related changes.

To waive bioequivalence requirements for lower strengths of a dosage form

To support waivers for other bioequivalence requirements.

Dissolution profiles may be considered similar by virtue of (1) overall profile similarity (2) similarity at every dissolution sample time point. The dissolution profile comparison

May be carried out using model independent or model dependent methods.

Model independent approach using a similarity factor

A simple model independent approach uses a difference factor (f1) and a similarity factor (f2) to compare dissolution profiles. The difference factor (f1) calculates the percent (%) difference between the two curves at each time point and is a measurement of the relative error between the two curves:

Were n is the number of time points, RT is the dissolution value of the reference (per change) batch at time t, and Tt is the dissolution value of the test (post change) batch at time t.

The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

A specific procedure to determine difference and similarity factors is as follows:

Determine the dissolution profile of two products (12 units each) of the test (post change) and reference (pre change) products.

Using the mean dissolution values from both curves at each time interval, calculate the difference factor (f1) and similarity factor (f2using the above equation.

For curves to be considered similar, f1, values should be close to o, and f2should be close to 100. generally, f2 values up to 15 (0-15) and f2 values greater than 50 (50-100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test (post change) and reference (pre change) products.

This model independent method is most suitable for dissolution profile comparison when three or four or more dissolution time points are available. As further suggestions for the general approach, the following recommendations should be considered:

The dissolution measurements of the test and reference batches should be made under exactly the same conditions. The dissolution time points for both the profiles should be the same (e. g.., 15, 30, 45, 60 minutes). The reference batch used should be most recently manufactured pre change product

Only one measurement should be considered after 85% dissolution of both the products.

To allow use of mean data, the percent coefficient of variation at the time points (e. g., 15minutes) should not be more than 10%

The mean dissolution values for r1can are derived either from (1) last t pre change (reference) batch or (2) last two or more consequently manufactured pre change batches. (Francesco C et al, 2005)

CONCLUSION

In this article we have been review fast dissolving tablets pharmacokinetics, pharmacodynamics, and advantages. Move over we have been discussing about drugs used, evaluation test, patented technologies and other

technologies in preparation of fast dissolving tablets. Here by we are concluding that fast dissolving tablets one innovative route for various drugs to increase their efficacy.

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