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APPRAISAL ON ORAL DISINTEGRATING TABLET: A REVIEW

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ABSTRACT
Fast disintegrating tablets (FDTs) are those solid dosage forms when put on tongue, disintegrate or dissolve instantaneously, releasing the drug, within a few seconds without the need of water. Fast disintegrating tablets (FDTs) aim for designing dosage forms, convenient to be manufactured and administered, free of side effects, offering immediate release and enhanced bioavailability, to achieve better patient compliance. Fast disintegrating tablets have been formulated for pediatric, geriatric, and bedridden patients and for active patients who are busy and traveling and may not have access to water. Such formulations provide an opportunity to persons which have difficulty in taking conventional oral dosage form.(viz., solutions, suspensions, tablets, and capsules).The current article is focused on ideal requirements, need for development of FDTs, superdisintegrants employed, various technologies developed for FDTs, patented technologies like Wowtab, Durasolv, Orasolv, Flashtab, Zydis, Frosta technology, Sheaform, Ceaform technology, Nanocrystal technology which have gained importance in international market, evaluation methods and various marketed products.

KEYWORDS: Fast disintegrating tablets (FDTs), Superdisintegrants, Enhanced bioavailability, Evaluation of tablets, Patented technology.

INTRODUCTION

Drug delivery system is an efficient tool for enhancing market extending product life cycles and creating opportunities. Recently, fast disintegrating drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance. FDA defined Fast dissolving/disintegrating tablets (FDDTs) are "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue".

Fast disintegrating tablets (FDT) are also known as fast dissolving, mouth dissolving, rapid-dissolve, quick disintegrating, orally disintegrating, rapimelt, fast melts, or dispersible, melt-in-mouth, quick dissolving, porous tablets, EFVDAS.[1]

Ideal Characteristics of Fast Dissolving Delivery System

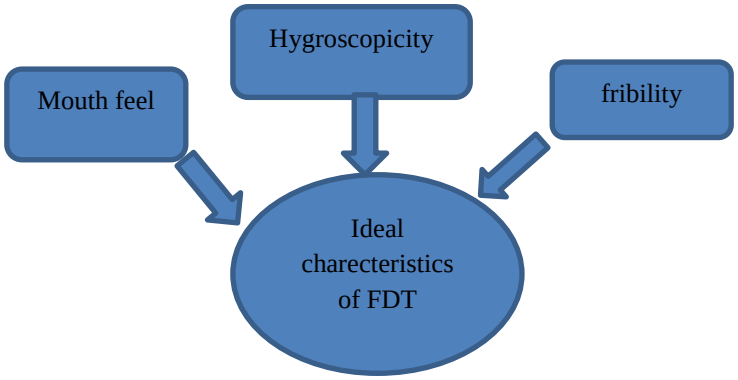

FIG:1

Criteria for selection of drug for Fast Dissolving Tablets

- ✓ Drug should have to permeate through oral mucosal tissue.
- ✓ Fast dissolving tablets dose should be lower than 20mg.
- ✓ Drug should be partially nonionized at pH in oralcavity.
- ✓ Drug should posses log P>2.

Administration of Mouth Dissolving Tablets

Mouth dissolving phenomenon is very supportive routes for life-threating disease patients like nervous illness, radioactivity therapy, Parkinson's disease, ADIS which face the dysphasia condition .Administration of new dosage formulation like effervescent tablet, dry syrups to these patients involves distress due to the necessary intake of water.[2]

Advantages of Fast Disintegrating Tablets

Accurate dosing: Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for pediatric and geriatric patients.

Enhanced bioavailability: Bioavailability of drugs is enhanced due to absorption from mouth, pharynx and esophagus.

Rapid action: Fast onset of therapeutic action as tablet gets disintegrated rapidly along with quick dissolution and absorption in oral cavity.

Patient compliance: No need of water to swallow the dosage form. Hence, it is convenient for patients who are traveling and do not have immediate access to water.

Ease of administration: Convenient to administer specially for geriatric, pediatric, mentally disabled and bed ridden patients who have difficulty in swallowing.

Obstruction free: No risk of suffocation in airways due to physical obstruction when swallowed, thus providing improved safety and compliance.

Enhanced palatability: Good mouth feel, especially for pediatric patients as taste masking technique is used to avoid the bitter taste of drug.

Simple packaging: No specific packaging required. It can be packaged in push through blisters.

Business avenue: Provide new business opportunities in the form of product differentiation, line extension, uniqueness and life cycle management.

Cost effective: Conventional processing and packaging equipments allow the manufacturing of tablets at low cost.[3,4]

Biopharmaceutical Consideratio

Pharmacokinetics

Study has done on absorption, distribution, metabolis m and excretion in this consideration. Drug attains therapeutic level after absorption and therefore elicits pharmacological effect, so both rate and extend of absorption is important. There is delay in disintegration and therefore dissolution in conventional dosage form while FDTs is rapidly disintegrates in oral cavity and dissolution is rapid. Due to disintegration of FDTs in mouth absorption in started from mouth, pharynx and esophagus. Some factors like age, GI pH, and blood flow through GI are taken into consideration, because elders may be considered as separate unique Medicare population. There are many factors on which drug distribution depends like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs increase.

Pharmacodynamics

Drug receptor interaction impaired in elderly as well as in young adult due to undue development of organ. Decreased ability of the body to respond baro reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin. Decreased sensitivity of the CVS to β-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 illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed.[5]

Mechanism

Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The solubility of a drug mainly depends on physiochemical properties of the drug. The rate of drug dissolution is greatly influenced by disintegration of the tablet.

Disintegrants are important excipient of the tablet formulation, they are always added to tablet to induce breakup of tablet when they are comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants.

The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together.[6]

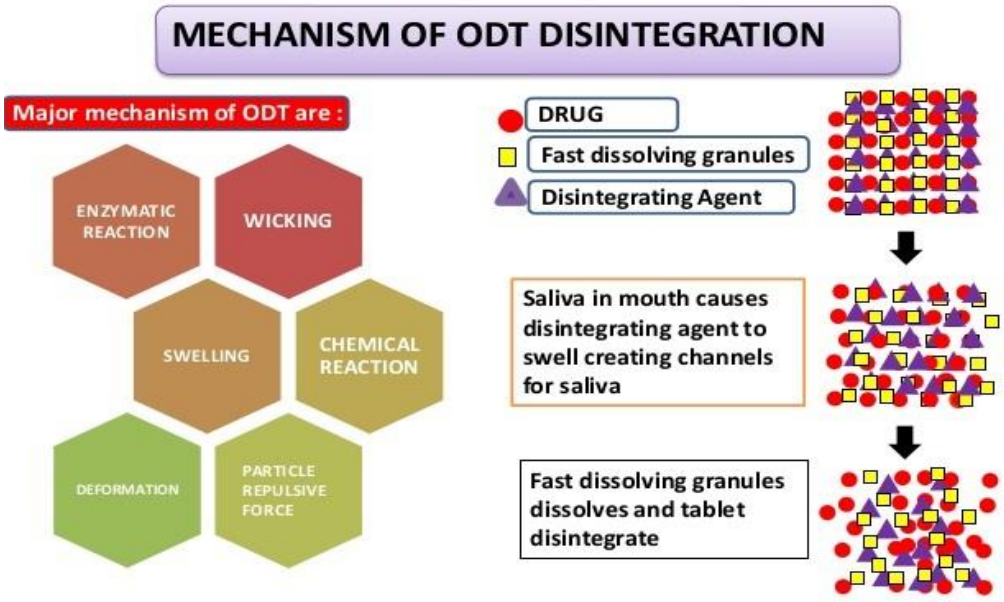

Fig 2.

Excipients used in the formulation of FDT

1. Bulking agents.
2. Emulsifying Agents.
3. Lubricants.
4. Flavors and Sweeteners.
5. Gas producing disintegrants.
6. Super disintegrants.

Excipients used in the formulation of FDT

Excipients balance the properties of the actives in fast-melting tablets. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives Excipients are general and can be used for a broad range of actives, except some actives that require masking agents.

Bulking agents: Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides adding bulk also reduces the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitols, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolystate for higher aqueous solubility and good sensory perception. Mannitol in particular has high aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition.

Emulsifying Agents: Emulsifying agents are important excipients for formulating fast-melting tablets they aid in rapid disintegration and drug release without chewing, swallowing or drinking water. A wide range of emulsifiers is recommended for fast-tablet formulation, including alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These agents can be incorporated in the range of 0.05 percent to about 15 percent by weight of the final composition.

Lubricants: They remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

Flavors and Sweeteners: Flavors and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients. Both natural and synthetic flavors can be used to improve the organoleptic characteristic of fast-melting tablets. Formulators can choose from a wide range of sweeteners including sugar, dextrose and fructose, as well as non-nutritive sweeteners such as aspartame, sodium saccharin, sugar alcohols and sucralose. The addition of sweeteners contributes a pleasant taste as well as bulk to the composition.

Gas producing disintegrants: Gas producing disintegrants are used especially where extra rapid disintegration or readily soluble formulation is required. They have also been found of value when poor disintegration characteristics have resisted other methods of improvement. Composition is based upon the same principles as those used for effervescent tablets, the most common being mixtures of citric & tartaric acids plus carbonates or bicarbonates. In many instances lower concentration can be used with gas producing disintegrants than are required by other disintegrating agents. Certain peroxides that release oxygen have been tried, but they do not perform as well as those releasing carbon dioxide.[7]

Super disintegrants: Superdisintegrants are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective superdisintegrants provide

improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs, some commonly used superdisintegrants are cross linked carboxymethyl cellulose (crosscarmellose), sodium starch glycolate, polyvinylpyrrolidone, sago starch, isphagula husk, calcium silicate, soy polysaccharides etc.

Advantages of Superdisintegrants

- ✓ Effective in lower concentrations.
- ✓ Compatible with commonly used therapeutical agents and excipients.
- ✓ Less effect on compressibility and flowability.
- ✓ Remarkable tendency on wetting causing rapid disintegration.
- ✓ Work equally effective in hydrophilic and hydrophobic formulations.
- ✓ More effective intragranularly.
- ✓ Does not stick to the punches and dyes.[8]

Mechanism of Superdisintegrants

There are four major mechanisms for tablets disintegration as follows.

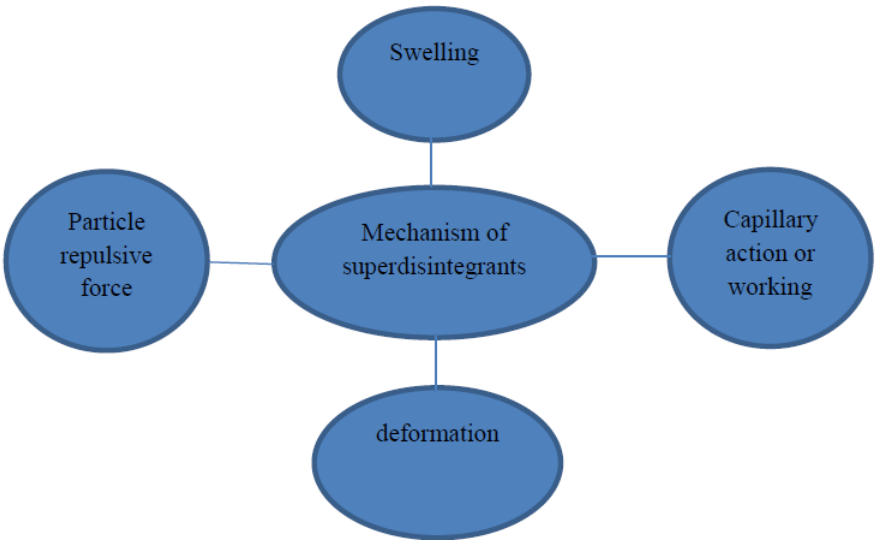

Fig 3.

Swelling: The most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

Porosity and capillary action (Wicking): Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tabletting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles. Water is pulled by disintegrant Particles swell and breaks up and reduced the physical the matrix form within bonding force between particles.

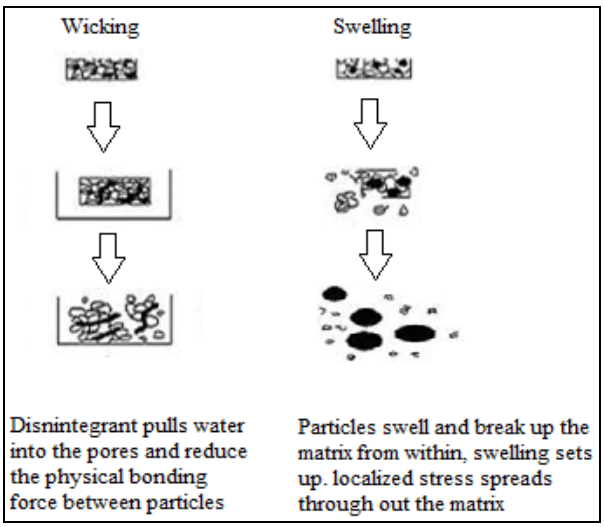

Fig. 4.

Due to disintegrating particle/particle repulsive forces-: Another mechanism of disintegrating attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non-swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it.

Researchers found that repulsion is secondary to wicking.

Due to deformation: During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.[9]

FIG: 5.

Patented technology for the formulation of FDT

Zydis Technology[1]: Zydis was introduced By R. P. Scherer Corporation in 1986. The Zydis process requires the active ingredient to be dissolved or suspended in an aqueous solution of water-soluble structure forming additives then the mixture is poured into the preformed blister pockets of a laminate film and freeze-dried. This results in a tablet shaped dosage form that spontaneously disintegrates in mouth in seconds. The two most commonly used structural additives are gelatin and mannitol although some other (e.g., starches, gums, etc.) may be used depending on the properties of the active ingredient. As a general rule, the best physical characteristics are achieved by using a mixture of a water-soluble polymer and a crystalline sugar alcohol or amino acid at a typical combined concentration of 10% w/w in the matrix solution. The polymer gives the strength and resilience while the crystalline component gives the hardness and texture.[10]

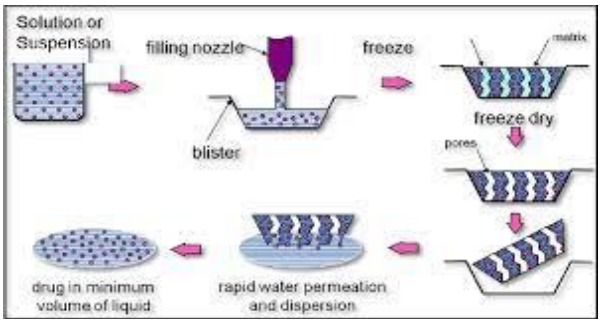

Fig 6.

Orasolv Technology[1]: CIMA labs have developed Orasolv Technology. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable.[11]

OraQuick: KV Pharmaceutical claims its microsphere technology, known as MicroMask, has superior mouthfeel over taste-masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also, lower heat of production than alternative fast-dissolving/disintegrating technologies makes OraQuick appropriate for heat-sensitive drugs. KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking. OraQuick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the OraQuick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives.

Quick-Dis Technology: Lavipharm Laboratories Inc. (Lavipharm) has invented an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intraoral drug delivery system, trademarked Quick- Dis™, is Lavipharm's proprietary patented technology and is a thin, flexible, and quick-dissolving film. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. The Quick-Dis™ drug delivery system can be provided in various packaging configurations, ranging from unit dose pouches to multiple-dose blister packages. The typical disintegration time, which is defined as the time at which the film begins to break when brought into contact with water, is only 5 to 10 seconds for the Quick-Dis™ film with a thickness of 2 mm. The dissolving time, which is defined as the time at which not less than 80% of the tested film is dissolved in aqueous media, is around 30 seconds for Quick Dis™ film with a thickness of 2 mm. The typical release profile of an active ingredient exhibited by a Quick-Dis™ drug delivery system is 50% released within 30 seconds and 95% within 1 minute.[12]

Durasolv Technology: DuraSolv is Cima's second-generation fast-dissolving/ disintegrating tablet formulation. Produced in a fashion similar to OraSolv, DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tabletting. DuraSolv tablets are prepared by using conventional tabletting equipment and have

good rigidity (friability less than that 2%). The DuraSolv product is thus produced in a faster and more costeffective manner. DuraSolv is so durable that it can be packaged in traditional blister packaging, pouches or vials. One disadvantage of DuraSolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction.

Unlike OraSolv, the structural integrity of any taste masking may be compromised with high drug doses. The drug powder coating in DuraSolv may become fractured during compaction, exposing the bitter-tasting drug to a patient's taste buds. Therefore, the DuraSolv technology is best suited for formulations including relatively small doses of active compound.

Flash Dose Technology: By this technology sugar based matrix known as floss which made from combination of excipients either alone or in combination of drugs. Nurofen meltelt, a new form of ibuporfen is based on same technology.

Flashtab technology: Prographarm patented this technology in which tablet consists of active ingredients in form of microcrystals. Rest of all procedure is followed in conventional technology.

Sheaform Technology: This technology makes Sheaform matrix consisting of floss preparation. Floss is produced by subjecting to a feed shock containing a sugar to flash heat processing.

Ceform Technology: In this technology microspheres containing active ingredient are prepared. Basic requirement of this technology is placing dry powder containing either pure drug or special blend of drug and excipients. The microspheres then mixed and compressed into previously selected oral dosage form.

Wowtab Technology: Wowtab Technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water ". In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low moldability saccharide and granulated with a high moldability saccharide and compressed into tablet.

Lyoc tech: This is patented technology of Laboratories L. Lafon, Maisons Alfort, France. It utilizes a freeze drying process but differ from Zydis in that the product is frozen on the freeze dryer shelves.

To prevent inhomogeneity by sedimentation during this process, these formulations require a large proportion of undissolved inert filler (mannitol), to increase the viscosity of the inprocess suspension. The high proportion of filler reduces the potential porosity of the dried dosage form and results in denser tablets with disintegration rates that are comparable with the loosely compressed fast melt formulations.[13]

Evaluation of Mouth Dissolving Tablet

Size and Shape: The size and shape of the tablet can be dimensionally described, monitored and controlled.

Tablet thickness: Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

Uniformity of weight: I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. Average weight of Tablets (mg) Maximum percentage difference allowed 130 or less 10 130-324 7.5 More than 324 5.

Tablet hardness: Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester.

Friability: It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. A pre weighed tablet was placed in the friabilator. Friabilator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 minutes. At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as.

%Friability = loss in weight / Initial weight x 100

In-Vivo Disintegration test: The test was carried out on 6 tablets using the apparatus specified in I.P.-1996 distilled water at 37°C ± 2°C was used as a disintegration media and the time in second is taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

Wetting time: The method reported by Yunixia et al., was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined.

In vitro dispersion time: In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.[14, 15]

CONCLUSION

Due to the increasing demand of novel drug delivery, the fast disintegrating drug delivery system has become one of the mile stone in the novel drug delivery system. The introduction of fast dissolving drug delivery system has encountered the delivery of conventional dosage form.

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