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FAST DISSOLVING SYSTEMS – AN ALTERNATIVE APPROACH FOR ENHANCED THERAPEUTIC ACTION

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ABSTRACT

From the past years the advancement of pharmaceutical technology has presented the change of dosage forms for patients who may have difficulty in swallowing of conventional tablets. The systems which disintegrate and release the active ingredient quickly and that do not require water to aid swallowing are fast dissolving drug delivery systems (FDDDSs). Amid the FDDDS, the fast disintegrating tablets (FDTs) are the attendant defensible form of drug delivery system because of its convenience of self-administration and compactness. The traditional capsules and tablets administration has shown difficulty in swallowing for pediatric, geriatric, and uncooperative patients. The basic creep up on used in blooming of FDT is the use of superdisintegrants which bestow immediate disintegration and thereby releasing the drug in saliva. Oral administration of bitter drugs with an acceptable degree of palatability can be attained by taste masking. These promulgation reviews the applications and technologies intricate in the formulation of FDDDS especially focused on FDTs.

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INTRODUCTION

In current decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. To improve the ease of administration many dosage forms are obtained and among them most widely preferred commercial products are fast dissolving tablets. The concept of fast dissolving drug delivery systems emerged from the desire to provide the patient with conventional means of taking their damage. These kind of fast dissolving tablets are good for those patients who have difficulty to swallow, especially geriatric & pediatric patients. The main criterion for fast dissolving tablets is to dissolve in the oral cavity saliva within 15 to 60 seconds without the need of water and should have a pleasant mouth feel. The concept of FDTs came into view with an objective of more patient compliance. The main proposal of the present review is to study the ideal properties, advantages, conventional and patented technologies, marketed formulations in FDTs and evaluation of FDTs.[1-3.]

SALIENT FEATURES OF FAST DISSOLVING SYSTEMS

- Effortless administration to the patient who cannot swallow, such as the aged, stroke victims, bedridden patients, a patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- No necessary of a water to swallow the dosage form, which is an immensely convenient feature for patients who are travelling and do not have immediate access to water.
- The quick onset of action is produced by rapid dissolution and absorption of the drug.
- Few drugs are engrossed from the mouth, pharynx and oesophagus as the saliva proceed below into the stomach. In such cases, the bioavailability of the drug is enhanced.
- Pre-gastric absorption can result in improved bioavailability and as a result of reduced dose; improve clinical performance through a reduction of unwanted effects.
- Good mouth feel property helps to change the perception of medication as a bitter pill, particularly in the pediatric patient.
- The risk of choking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- A new business opportunity like product differentiation, product promotion, patent extensions and life cycle management.
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra-rapid onset of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Stability for a longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines the advantage of the solid dosage form in terms of stability along with liquid dosage form in terms of bioavailability[4].

ADVANTAGES OF FAST-DISSOLVING SYSTEMS

- Ease of administration to geriatric, pediatric, mentally disabled, and bed-ridden patients who have difficulty in swallowing the tablet
- The FDTs do not need water for swallowing, unlike conventional dosage forms. This is very easy for patients who are travelling or do not have immediate access to water, and thus, provide enhanced patient compliance.
- Being unit solid dosage forms provide the advantage of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for pediatric and geriatric patients.
- Bioavailability of drugs is enhanced due to absorption from mouth, pharynx, and oesophagus.
- Pregastric absorption can result in improved bioavailability and because of reduced dose, improved clinical performance through a reduction of unwanted effects.
- Rapid onset of therapeutic action as the tablet is disintegrated rapidly along with quick dissolution and absorption in the oral cavity.
- Good mouth feel, especially for pediatric patients as taste-masking technique issued to avoid the bitter taste of drugs.
- Minimum risk of suffocation in airways due to physical obstruction, when FDTs are swallowed, thus they provide improved safety and compliance with their administrations.
- Rapid drug therapy intervention is possible.
- Conventional processing and packaging equipment allow the manufacturing of tablets at the low cost.
- No specific packaging is required. It can be packaged in push-through blisters.
- Provide new business opportunities in the form of product differentiation, patent-life extension, uniqueness, line extension, and lifecycle management, and exclusivity of product promotion [5-6]

LIMITATIONS OF FAST DISSOLVING SYSTEMS

- Drugs with relatively larger doses are not suitable for formulation into fast-dissolving systems e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500mg of the drug.
- Patients who concurrently take anticholinergic medications may not be the best candidates for FDT[7].

IDEAL PROPERTIES OF FAST DISSOLVING SYSTEMS

- Fast-dissolving systems does not require for administration.
- Fast-dissolving systems easily dissolve or disintegrate in saliva within a few seconds.
- Fast-dissolving systems have a pleasing taste.
- Leave negligible or no residue in the mouth when administered.
- Be portable and easy to transport.
- Be able to be manufactured in a simple conventional manner at low cost.
- They are less sensitive to environmental conditions like temperature, humidity etc. [8-10]

CHALLENGES FOR DEVELOPMENT OF FAST DISSOLVING SYSTEMS

Mechanical strength and disintegration time

It is obvious that decrease in the disintegration time decreases the mechanical strength. So an acceptable compromise between these two parameters is always necessary. Fast-dissolving systems are formulated to achieve disintegration time usually less than a minute. While doing so, sustaining a good mechanical strength is a prime challenge.

Taste Masking

As most drugs are unappetizing, rapid disintegrating drug delivery systems generally contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in the patient's oral cavity, so releasing the active ingredients which come in contact with the taste buds; therefore, taste- masking of the drugs becomes critical to patient compliance.

Aqueous solubility

Water-soluble drugs pose various formula ion challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure over the sublimates ion process. Such collapse sometimes can be stopped by using various matrix-forming excipients such as mannitol which induces crystallinity and hence, it imparts rigidity.

Hygroscopicity

Hygroscopicity is, of course, an essential characteristic of a powder. It can be presented, roughly, for a fairly soluble compound that the hygroscopicity is related to its solubility. Fast-dissolving systems should have low sensitivity to humidity. This problem can be especially challenging because many highly water-soluble excipients are used in the formulation to enhance fast-dissolving properties as well as to create a good mouth feel. Those highly water-soluble excipients are susceptible to moisture; some will even deliquesce thigh humidity. A good package design or another strategy should be created to protect FDTs from various environmental conditions.

Amount of drug

The application of methods used for FDTs is limited by the amount of drug that can be given into each unit dose. For lyophilized dosage forms, the drug dose must be less than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating fast-dissolving oral films or wafers.

Mouth feel

The particles generated after the disintegration of the FDTs should be as small as possible. Moreover, the addition of flavours and cooling agents like menthol improve the mouth feel.

Sensitivity to environmental conditions

FDTs should exhibit low sensitivity to environmental conditions such as humidity and temperature as most of the materials used in FDTs are meant to dissolve in a minimum quantity of water.

Cost

The technology used for FDTs should be acceptable in terms of the cost of the final product. Methods like Zydis and Orasolv that require special methods and specific packaging increase the cost to a remarkable extent.

Tablet strength, Friability and porosity

In order to pass fast disintegrating tablets to disintegrate in the mouth, they are made of either very porous or soft moulded matrices or compressed into tablets with very less compression force, which makes the tablets friable and/or brittle, which are hard to handle, often requiring specialized peel-off blister packaging. [11-21]

CRITERIA OF DRUG SELECTION

The criteria for drug selection for fast dissolving system include

- The drug should have moderately non- ionized at the oral cavities pH.
- The drug should have low to moderate molecular weight.
- The drug should have ability to permeate the oral mucosa.
- The drug should have the ability to diffuse and partition into the epithelium of the upper GIT.
- The drug should have good stability in water and saliva.
- Drugs which have lower bioavailability are good candidates for fast-dissolving systems.
- Short half-life of drugs and frequent dosing drugs are unsuitable for fast-dissolving systems.
- Drugs with very bitter taste and odoured drugs are unsuitable for fast-dissolving systems. Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs.
- Drugs having the capability to diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferably > 2); those able to permeate oral mucosal tissue are shown ideal for FDT formulations. Drugs which require controlled or sustained release are unsuitable candidates of fast dissolving oral dosage forms. [22]

CRITERIA FOR SLECTION OF EXCIPIENTS IN THE FORMULATION OF FAST-DISSOLVING SYSTEMS

The ideal characteristics of excipients for fast dissolving systems include

- Quick disintegration
- No interaction with drug and other excipients.
- No interference in the efficacy and organoleptic properties of the fast-dissolving systems.
- Care should be taken in selection of binder as it affects the integrity and stability of the fast dissolving system.
- The melting point of the excipients used in the formulation of fast-dissolving systems should be in the range of 30-35ºC.

EXCIPIENTS USED IN THE FORMULATION OF FAST DISSOLVING SYSTEMS

Excipients balance the properties of the actives in fast-melting tablets. This claims a thorough understanding of the chemistry of these excipients to prevent interaction with the active ingredients. Determining the cost of these ingredients is an additional issue that needs to be discussed by formulators. The position of excipients is important in the formulation of fast-melting tablets. These inactive food-grade ingredients, when corporate in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents.

Bulking agents

Bulking agents enhance the textural characteristics that in turn strengthen the disintegration in the mouth, besides; adding bulk also lowers the concentration of the active ingredient in the composition. The suggested bulking agents for this delivery system should be more sugar based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolystate for greater aqueous solubility and good sensory perception. Mannitol, in particular, has better 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.

Flavours and Sweeteners

Flavours and taste-masking agents make the products more patentable and pleasing for patients. The addition of these ingredients assists in reducing bitterness and undesirable tastes of some active ingredients. Both natural and synthetic flavours can be used to enhance the organoleptic characteristics of fast-dissolving tablets. Formulators can prefer 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 gives a pleasant taste as well as bulk to the composition.

Gas-producing disintegrants

Gas-producing disintegrants are used specifically where extra rapid disintegration or readily soluble formulation is required. They have also been found of value when poor disintegration characteristics have resisted other techniques of improvement. Care should be taken during tabletting, particularly on moisture level. The 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 that are required by other disintegrating agents.

Super disintegrants

Super disintegrants are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the super disintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective super disintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs. Some commonly used super disintegrants are cross-linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate, polyvinyl pyrrolidone, sago starch, isphagula husk, calcium silicate, soy polysaccharides etc. [23-28]

ADVANTAGES OF SUPERDISINTEGRANTS

- Effective in lower concentrations.
- Less effect on compressibility and flowability.
- The remarkable tendency on wetting causing rapid disintegration.
- Does not stick to the punches and dyes. [29, 30]

VARIOUS TECHNIQUES FOR PREPARATION OF FAST DISSOLVING TABLETS (FDTs):

Techniques for the preparation of FDTs include

Non-Patented Technology:

Various non-patented technologies include

Freeze-Drying or Lyophilization

Freeze drying is the technique in which water is sublimed from the product after it is frozen. This technique forms an amorphous porous structure that can dissolve immediately. Using this technique an essential procedure involved in the manufacture of FDT, in an aqueous solution of a carrier/polymer the active drug is dissolved or dispersed. The mixture is weighed and poured on the walls of the preformed blister packs. The trays holding the blister packs are passed through a liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are kept in refrigerated cabinets to continue the freeze-drying. After freeze-drying, the aluminum foil backing is applied to a blister-sealing machine. Finally, the blisters are packaged and shipped. The freeze-drying technique has demonstrated enhanced absorption and better bioavailability. The major disadvantages of lyophilization technique are that it is expensive and time-consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

Tablet Molding

The moulding technique is of two types i.e., solvent method and heat method. The solvent method involves moistening the powder blend with a hydroalcoholic solvent followed by compression at low pressures in the moulded plates to get a wetted mass (compression moulding). The solvent is then eliminated by air-drying. The tablets manufactured in this manner are less rigid than compressed tablets and posses a porous structure that accelerates dissolution. The heat moulding technique involves preparation of a suspension that consists of a drug, agar and sugar (e.g. mannitol or lactose). The suspension was poured in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30^{o}C under vacuum. The mechanical strength of moulded tablets is an element of great concern. Binding agents, which enhance the mechanical strength of the tablets, need to be incorporated. Taste masking is an added complication to this technology. The taste masked drug particles were prepared by spray 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 lyophilization technique, tablets produced by the moulding technique are easier to scale up for industrial manufacture.

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 croscarmellose or crospovidone is used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in an aqueous medium.

The formulation contained a bulking agent like mannitol and lactose, a super disintegrant like sodium starch glycolate & croscarmellose sodium and an acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder is then compressed into tablets and showed hasty disintegration and increased dissolution.

Sublimation

To develop a porous matrix, volatile ingredients are incorporated in the formulations, which are 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 packed along with other excipients into a tablet. This volatile material is then eliminated by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have recorded to usually disintegrate in 10-20 sec. Even solvents like cyclohexane, benzene can be utilized as pore forming agents.

Direct compression

Direct compression produces the simplest and most cost-effective tablet manufacturing technique. In this process, tablets are prepared directly by compression of the mixture of drug and excipients without any preliminary treatment. The mixture that is to be compressed must have good flow properties.

Nanonization

A recently developed Nanomelt technology involves a reduction in the particle size of a drug to nanosize by milling the drug using a proprietary wet-milling technique. On selected stabilizers, the nanocrystals of the drug are stabilized against agglomeration by surface adsorption which is then incorporated into FDTs. This process is especially advantageous for poorly water-soluble drugs. Other advantages of this technology include fast disintegration/ dissolution of nanoparticles leading to the reduction in dose, enhanced absorption, better bioavailability, cost-effective manufacturing process, conventional packaging due to exceptional durability and the wide range of doses (up to 200 mg of drug per unit).

Fast Dissolving Films

In this technique, a non-aqueous solution is prepared to contain water-soluble film-forming polymer (pullulan, carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxyl ethyl cellulose, hydroxy propyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste masking ingredients, which is allowed to form a film after evaporation of the solvent In instance of a bitter drug, resin adsorbate or coated microparticles of the drug can be incorporated into the film. This film, when kept in the mouth, melts or dissolves immediately, releasing the drug in solution or suspension form. The features of this system include paper-thin films of size less than 2x2 inches, dissolution in 5 sec, instant drug delivery and flavoured after taste. [31-36]

PATENTED TECHNOLOGY FOR THE FORMULATION OF FDT

Zydis Technology

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 the 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 the 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.

Orasolv Technology

CIMA labs have developed Orasolv Technology. In this system, the active medicament is taste masked. It also contains the 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 are used to produce the tablets. The tablets produced are soft and friable.

OraQuic

KV Pharmaceutical claims its microsphere technology, known as MicroMask, has the superior mouthfeel over taste-masking alternatives. The taste masking process does not utilize solvents of any kind, which therefore leads to faster as well as more efficient production. KV Pharmaceutical also alleges that the matrix that surrounds and protects the drug powder in microencapsulated particles which are more pliable and implicates the tablets that 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. The current scenario in the market is that there are no products available with OraQuick technology, but KV Pharmaceutical has products in development like analgesics, scheduled drugs, cough and cold, psychotropic's, and anti-infective.

Quick-Dis Technology

The ideal intraoral fast-dissolving drug delivery system was invented by Lavipharm Laboratories Inc. (Lavipharm), which satisfies the unmet needs of the market. Quick- Dis™ is Lavipharm's proprietary patented technology that trademarked the novel intraoral drug delivery system which is a thin, flexible, and quick-dissolving film. The film is kept on the top or the floor of the tongue. It is sustained at the site of application which rapidly releases the active agent for local and/or systemic absorption. The Quick-Dis™ drug delivery system can be dispensed into various packaging configurations, ranging from unit dose pouches to multiple-dose blister packages. The essential disintegration time, which is known 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 characteristic 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.

Durasolv Technology

DuraSolv is Cima's second-generation fast-dissolving/ disintegrating tablet formulation. By using conventional tabletting equipment, DuraSolv tablets are prepared with good rigidity (friability less than that 2%). The DuraSolv product is thus given in a faster and more cost-effective manner. DuraSolv is so stable that it can be packaged in traditional blister packaging, pouches or vials. One detriment of DuraSolv is that the technology is not adaptable 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 conceded with high drug doses. The drug powder coating in DuraSolv may develop fractures 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 the active compound.

Flash Dose Technology

By this technology sugar-based matrix known as floss which made from a combination of excipients either alone or in the combination of drugs. Nurofen meltelt, a new form of aceclofenac is based on the same technology.

Flashtab technology

This technology is patented by prographarm in which tablet consists of active ingredients in form of microcrystals. Rest of all procedure is followed in the conventional technology.

Shea form Technology

This technology makes Shea form matrix consisting of floss preparation. Floss is obtained by subjecting to a feed shock containing a sugar to flash heat processing.

Ceform Technology

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

Wowtab Technology

Wowtab Technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water ". In this process, the combination of low mouldability 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 the tablet.

Lyoc tech

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

Pharmaburst technology

Pharmaburst™ is a "Swift Dissolve" delivery system patented by SPI Pharma. Pharmaburst is a co-processed excipient system with specific excipients, which allows rapid disintegration. Saccharides are used to obtain rapid melting tablet.

Frosta technology

Frosta technology is patented by Akina. This technology applies the theory of formulating plastic granules and compressing them at low pressure to get strong tablets with high porosity. Plastic granules confined of porous and plastic material, water penetration enhancer, and binder. The process involves mixing the porous plastic material with water penetration enhancer followed by granulating with a binder. The tablets attained have excellent hardness and expeditious disintegration time ranging from 15 to 30 sec depending on the size of a tablet.

The process involves mixing the porous plastic material with water penetration enhancer followed by granulating with a binder. The tablets obtained have excellent hardness and expeditious disintegration time ranging from 15 to 30 sec depending on the size of a tablet.

Advatab

AdvaTab Tablets disintegrate briskly in the mouth, difficulty in less than 30 seconds, to enable for convenient oral drug administration without water. These tablets are suited to those patients that overcome the difficulty in swallowing capsules and tablets. From FDT technologies, AdvaTab is a distinct feature as it can be combined with Eurand's complimentary particle technologies like its world-leading Microcaps® taste-masking technology and its Diffucaps®, controlled release technology. AdvaTab together with Microcaps develop products that offer the dual advantage of a patient compliance, along with a taste and smooth mouth feel. This is a censorious advantage as the unpleasant taste of drugs is an appreciable restriction in the application of other FDT technologies[37, 38].

CONCLUSION

Fast dissolving drug delivery systems have shown better patient compliance, efficacy and also improved biopharmaceutical properties. FDT dosage forms accessed by some of these technologies have sufficient mechanical strength, quick dissolution /disintegration in the mouth. However, the difficulty in swallowing conventional tablets was experienced by geriatric and pediatric patients, which leads to low patient compliance. Scientists have developed innovative drug delivery systems known as FDT to overcome the difficulties. Their characteristic advantages helped geriatric and pediatric patients to administer the dosage form without water.

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