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A REVIEW on FAST DISSOLVING DRUG DELIVERY SYSTEM: TAKING ADVANTAGE of NANOFIBERS

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ABSTRACT

Fast-dissolving drug delivery systems (FDDDS) have recently gained attention and acceptance as a new oral drug delivery system. The aim of FDDDS is to enhance the safety and efficacy of conventional oral dosage forms and increase the patient compliance. This system was used initially in confectionery and oral care markets in the form of breath strips. Recently, large number of pharmaceutical industries are interested in this formulation due to high consumer acceptance. FDDDS is a type of drug delivery system that when is placed on tongue drug dissolves in the saliva and releases the drug immediately without the need of water or chewing. Due to unique properties, easy and effective preparation methods of electrospun nanofibers, they demonstrate great potential for developing various novel drug delivery systems (DDS). Currently, electrospun nanofiber-DDS are focused on preparation of drug-loaded nanofibers from different biodegradable polymers and various types of DDS. Although, electrospinning process and resulting drug-loaded nanofibers DDS have greater potential to be exploited.

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Introduction

The most commonly used path of administration of therapeutic agents is the oral path. The low cost and ease of administration of oral route result in high levels of patient compliance. Tablets and capsules are the most frequent oral solid dosage forms. However, it is difficult for pediatric and geriatric patients to swallow tablets and hard gelatin capsules that leads them to not take their medicines as prescribed [1,2]. Fast dissolving drug-delivery systems were developed in the late 1970's as an alternative to tablets, capsules and syrups for patients experiencing difficulties in swallowing traditional oral solid-dosage forms. They disintegrate and/or dissolve rapidly in the saliva without need for water. The main target populations for FDDDS have been pediatric, geriatric, and bedridden or developmentally disabled patients. Patients with constant nausea, who are traveling, or who have limited access to water are also good candidates for this system [3]. FDDDS offer benefits such as administration without water, rapid onset of action and convenience of dosing. Absorption of active ingredient through the oral mucosa may also enhance the bioavailability of drug [1,4]. Initially, FDDDS were formulated as pills [5] but, are now available in different forms such as films [6], wafers [7, 8], buccal [9, 10] and sublingual [11, 12] patches and electrospun nanofiber mats [12]. Electrospinning is a method where a polymer solution or melted polymer is spun by high potential electric field to produce smaller diameter fibers. This technique has gained a lot of attention in the last few years as it is capable of covering a wide range of fibers with submicron diameters. Several techniques are available to produce nanofibers but, electrospinning is gaining popularity as a simple process where operating condition and properties of polymer solution can be carefully monitored to produce highly porous structures of nanofibers. [13].

Advantages of Fast Dissolving Systems

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No special set up is required for manufacturing
 Larger surface area leads to rapid disintegration and dissolution in the oral cavity
 Promote the systemic absorption of APIs
 No need of water or a spoon for administration and no chewing required
 Site specific action and local action
 Noninvasive [14].

Disadvantages of FDDDS

High dose of active ingredient cannot be loaded into the FDDDS. Although the concentration level of active ingredient can be improved up to 50% per dose weight.
 tight packaging is required [14,15].

Mechanism of Action

Because of the presence of hydrophilic polymer and other excipients, as soon as the FDDDS is placed on patient's tongue or any oromucosal tissue the system gets wet and hydrates rapidly by saliva, and dissolves to release the drug for oromucosal absorption [15].

Materials for fast-dissolving systems

Certain materials are commonly used in preparation of all solvable systems, but a number of materials are specific to FDDDS [16].

General Ingredients

Drugs

Numerous classes of drugs can be formulated as mouth dissolving films including antiasthmatics (Salbutamol sulphate), antiulcer (Omeprazole), expectorants, antitussives, NSAID'S (Valdecoxib, Meloxicam) [17-20].

The ideal characteristics of a drug to be selected are as follow:

No bitter taste

Require Doses less than 30 mg

Small to moderate molecular weight

Good stability in water and saliva

Partially non-ionized at the oral cavities pH

Ability to diffuse and partition into the epithelium of the upper GIT ($\log P > 1$, or preferably > 2)

Saliva stimulating agents:

Saliva stimulating agents are employed to increase the production rate of saliva and to facilitate the disintegration of the rapid dissolving FDDDS formulations. Agents such as citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid can be employed as saliva stimulating agents. Citric acid is the most commonly used saliva stimulating agent [21-23].

Flavoring agents:

Flavoring agents are used in formulation to mask the unpleasant taste of drugs. The concentration of flavoring agent used is usually 10% w/w, however, the quantity required to mask the taste depends on the flavor type and the strength of flavoring agent. Various flavors such as peppermint flavor, cooling flavor, clove oil, bay oil, anise oil, eucalyptus oil, thyme oil and oil of bitter almonds could be used in the formulations [1,16,24].

Coloring Agent:

Because drugs and excipients may have different shades of color, a non-uniform appearance could be produced that is not attractive for the patients. Hence, coloring agents and opacifiers are employed to maintain a uniform color and appearance. Vast range of colors are available that includes FD&C colors, EU Colors, Natural Colors and custom Pantone-matched colors [25-28]

Surfactants:

Surfactants are employed in formulation as wetting or solubilising or dispersing agent to the film is getting dissolved within seconds and release the active agent rapidly. The commonly employed surfactants are polaxamer 407, bezathonium chloride, sodium lauryl sulfate, tweens, benzalkonium chloride, etc. Amongst the aforementioned surfactant the most predominantly used is polaxamer 407 [21,29].

Specific Ingredients:

Different fast dissolving dosage forms may have different ingredients depending on the dosage form required.

Polymers:

Polymers are used in formulation to obtain the desired film and nanofiber properties either alone or in combination. The water-soluble polymers result in rapid disintegration, good mouthfeel and mechanical properties to the films and nanofibers. The type and quantity of the polymer could affect the strength of the dosage. As the molecular weight of polymer formulation bases increase the rate of disintegration of the polymer decreases. Currently, both natural and synthetic polymers are employed in preparation of fast dissolving oral film (table 1).

Table 1: Various polymer used in preparation of FDDDS(30-35).

Polymer	Examples
Natural Polymers	Pullulan, Starch, Gelatin, Pectin, Sodium alginate, Maltodextrins, Polymerized Rosin
Synthetic Polymers	Hydroxy propyl methyl cellulose, Sodium Carboxy methyl cellulose, Poly ethylene oxide, Hydroxy propyl cellulose, Poly vinyl pyrrolidone, Poly vinyl alcohol

Plasticizers:

Plasticizer are used in formulation to improve the mechanical properties such as tensile strength and elongation to the film by decreasing the glass transition temperature of the polymer. Plasticizers could also decrease the brittleness of the strip that leads to an improvement of strip flexibility. The plasticizer is selected depending upon the type of solvent used and also its compatibility with the polymer. Plasticizers such as phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, low molecular weight polyethylene glycols, castor oil, citrate derivatives like tributyl, triethyl, acetyl citrate, triacetin and glycerol are routinely used in preparation of FDDDS. However, If plasticizer are not used properly it may lead to blooming, film cracking, splitting and peeling of the strip [30- 32].

Super Disintegrants:

To ensure the rapid disintegration of tablets that leads to enhance dissolution rate and quick absorption of drug, the super disintegrants excipients are employed in a concentration of 5-10%. A few example of these exepients are microcrystalline cellulose, hydroxypropyl methyl cellulose, modified starch, crosspovidone and crosscarmellose. Super disintegrants perform their function via different mechanisms; they could swell when in contact with water or increase the absorption of water into the dosage form [33-35].

Binder:

Binders are used mainly to retain the composition of fast melting tablets together during the compression stage. The commonly used binders are cellulosic polymers, povidones, polyvinyl alcohols, and acrylic polymers. Among the cellulosic polymers ethylcellulose, hydroxyl propyl cellulose (HPC), and (HPMC), are more preferable when use alone or in admixtures. The most commonly acrylic polymers used are the ammonio-methacrylate copolymer (Eudragit RL and RS), polyacrylate (Eudragit.NE), and polymethacrylate (Eudragit E). The proper selection of a binder or combination of binders is necessary to maintain the integrity and stability of the tablet. The melting temperature of the excipient should preferably be around 30–35 °C for faster melting properties. Furthermore, addition of binder results in smooth texture and disintegration characteristics to the system [36, 37].

Table2: Preparation Methods of FDDDS

Tablets	Films	Nanofibers
Freeze drying/lyophilization	Solvent casting	Drawing
Spray drying	Semi-solid casting	Template synthesis
Molding	Hot melt extrusion	Phase separation
Sublimation	Rolling	Self-assembly
Mass extrusion	Solid dispersion extrusion	Electrospinning
Direct compression	Compaction	
Cotton candy process		
Effervescent Method		

Lubricants:

Although lubricants are not an essential excipient, they could further help in making these tablets more palatable after they disintegrate in the mouth. Lubricants could remove the grittiness and assist in the transport mechanism of drug from the mouth down into the stomach. Though, it has been observed that hydrophobic lubricants such as calcium or magnesium stearate could delay the disintegration of the fast dissolving tablet therefore, it is recommended to use hydrophilic lubricants such as sodium or potassium benzoate for these dosage forms [38].

Fillers:

Selection of filler is important as it plays a role in determination of the disintegration time and it is also used to increase the bulk volume of the powder and the size of the tablet to form a tablet with suitable size for handling when the drug is very potent. The regularly used fillers are directly compressible spray dried mannitol, sorbitol, xylitol, pregelatinized starch [39].

Preparation Methods of FDS:

The method of preparation of various FDS dosage forms are different from each other. The methods are shown in Table 2 and each method is also explained briefly.

Nanofiber Preparation:

Different methods are available to prepare nanofibers and are listed in Table 2. The electrospinning technique is an ideal method to prepare nanofibers for research and commercial purposes. Nanofibers prepared by electrospinning methods are ideal to enhance dissolution and bioavailability of drugs. this technique has gained popularity due to its efficacy and superiority over traditional preparation methods. The following part discuss this method of preparation in detail.

Electrospinning:

The equipment required for electrospinning is simple, which consists of a high voltage electric source with positive or negative polarity, a syringe pump with capillaries or tubes to carry the solution from the syringe or pipette to the spinnerette, and a conducting collector like aluminum. The collector can be produced at varieties of shapes such as flat plate, rotating drum, etc, according to the requirements.

This process requires a high voltage electric field to produce electrically charged jets from polymer solution or melts that produces nanofibers upon drying by evaporating the solvent [40]. To collect the fibers highly charged fibers are field directed towards the oppositely charged collector, that can be a flat surface or a rotating drum. In conventional spinning method, the fiber is exposed to a group of tensile, gravitational, aerodynamic, rheological, and inertial forces. The spinning of fibers is achieved mainly by the tensile forces created in the axial direction of the flow of the polymer by the induced charges in the presence of an electric field [41].

Advantages of Electrospun Nanofibers:

recently, nanofibers have gained attention in research because of their pronounced micro and nano structural characteristics that allow the development of advanced materials with sophisticated applications. additionally, large surface area, small pore size, and the possibility of producing three dimensional structures makes nanofibers more attractive [40,41].

Process parameters and fiber morphology:

Parameters such as polymer solution feed rate, the electrospinning voltage, and the solution properties such as concentration, viscosity and surface tension can strongly affect the morphology of produced nanofibers. It has been shown that solutions with low molecular weight are tending to form beads rather than fibers and as the molecular weight of the solution increases the number of beads and droplet are reduced. The shape of the surface from which the electrospinning jet originates is observed to be changed by increasing the electrospinning voltage. As the electrospinning voltage increases, the volume of the droplet is decreased. The change in shape happens as a result of reduction in the stability of the initiating jet as the voltage increases which is correlated with an increase in numbers of bead defects formation along the electrospun fibers in particular surface area as a function of change in fiber size which is stimulated by changing the concentration of spinning solution. It has been shown that the diameter of electrospun fibers increases with solution concentration according to a power law relationship. Deitzel et al have also shown that an increase in viscosity or concentration of the solution results in formation of a larger and more uniform fiber diameter [42-45]. Surface tension is a critical factor for low viscosity solutions where they only form beads or beaded fibers whereas, above a critical concentration a continuous fibrous structure is produced and its morphology is influenced by the concentration of the solution. The solvent evaporates as the jet travels through the atmosphere and leaves a dry fiber on the collecting device. The jets break up into droplet for solutions with low viscosity but, when the viscosity of the solutions is high the jets travels to the collector as fiber jets by reducing the surface tension of a nanofiber solution and beadless fibers are achieved. Different solvent could contribute to different surface tensions and generally, solutions with high surface tensions could inhibits the electrospinning process due to instability of the jets and formation of sprayed droplets [43-46].

Conclusions

The popularity of fast dissolving dosage forms has increased enormously over the last decade. Many drugs have been formulated into marketed as FDDs using different methods. The main characteristics of the fast dissolving formulations is their fast disintegration, dissolution, or melting in the mouth. FDDs have superior patient acceptance and compliance and may offer enhanced biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms. currently, FDDs are commonly available as OTC products for treatment of allergies, cold, and flu symptoms. The FDDs offer promising potential because of the availability of new technologies combined with strong market acceptance and patient demand. Nanofibers are capable of forming highly porous mesh and their large surface-to-volume ratio could improve the performance for various applications. Electrospinning is the only methods capable of producing nanofibers from different materials in various fibrous assemblies. Due to high production rate and ease of the setup, electrospinning is widely used in both academia and industry. Sevral parameters such as polymer solution feed rate, the electrospinning voltage, and the solution properties such as concentration, viscosity and surface tension can affect the morphology of produced nanofibers. Various nanofibers for a wide range of applications such as energy storage, healthcare, biotechnology, environmental engineering, and defense and security can be made .

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