A Review on Fast Dissolving Systems: From Tablets to Nanofibers

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A Review on Fast Dissolving Systems: From Tablets to Nanofibers

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Abstract
Context: Oral administration of drugs remains the most common and preferred route for many active pharmaceutical ingredients (APIs). However, solid oral dosage forms may be limited for patients who have swallowing problems or fear of choking. Furthermore in the case of solid dosage forms, disintegration and dissolution of dosage forms are rate limiting steps mostly for hydrophobic drugs’ absorption and bioavailability. Liquid oral dosage forms such as syrups, emulsions or suspensions may be used to overcome these disadvantages but higher costs of their production and larger volume and dimensions of their packaging along with the lower precision in dose intake make the liquid oral dosage form less acceptable for patients and pharmaceutical industries.

Evidence Acquisition: In order to merge the advantages of both solid and liquid oral dosage forms, fast dissolving drug delivery systems have been developed over the years. The current review aimed to discuss the pros and cons of different preparations of oral fast dissolving dosage forms including tablets, films and nanofibers.

Results: Fast dissolving dosage forms rapidly dissolve in mouth without the need for additional liquid or chewing, providing ease of use for consumers, a fast absorption of drug, quick onset of action, and improved bioavailability. Various technologies to fabricate these dosage forms such as lyophilization, spray drying, solvent casting, hot melt extrusion, compaction and electrospinning are also addressed.

Conclusions: Fast dissolving drug delivery systems are the promising approach in oral drug delivery systems, which can provide patient compliance especially in case of pediatrics and geriatrics. They can also lead to quick action of drugs and enhanced bioavailability.

Keywords: Drug Delivery Systems, Solubility, Nanofibers, Tablets

1. Context
Oral route is the most preferred and acceptable route for patients and medical practitioners that is the reason pharmaceutical companies are encouraged to develop oral dosage forms for various patients (1, 2). Although, despite their convenience, development of dosage forms which can be used orally without the need for water and with fast acting properties is still in progress (3). Fast dissolving systems (FDS) are drug dosage forms which dissolve in the oral cavity without the need for drinking water or chewing (4). These systems were first developed in 1970 and became favorable very quickly (5, 6). At first these systems were in the form of tablets (7) but with the advancement of technology, different dosage forms such as films (8), wafers (9, 10), buccal (11, 12) and sublingual (13) patches (14) were formed. They can be used for local or systemic delivery of drugs.

2. Evidence Acquisition
The current review studies the major types of fast dissolving systems studied in research papers or commercially produced; including tablets, films and nanofibers. The advantages and disadvantages of these fast dissolving systems are addressed, and their preparation and evaluation techniques are discussed.

3. Results
3.1. General Advantages of Fast Dissolving Systems
As defined by their name, fast dissolving systems are used in conditions where there is a need for local or systemic fast delivery of drug, which makes them possible to be administered anytime and anywhere without water (4, 15-20). Due to these characteristics, fast dissolving dosage forms are suitable for geriatrics (21), pediatrics (21), people with swallowing problems, nauseated people, people who have fear of choking (22, 23) when swallowing a solid dosage form, bedridden patients and people who do not have access to water (24-26). Fast dissolving drug delivery systems have better patient compliance and may offer improved biopharmaceuti-
cal properties, improved efficacy and better safety compared to the conventional oral dosage forms (27). Rapid onset of action, improved stability, first pass effect bypass and increased bioavailability lead to increase the demand in pharmaceutical market (28, 29). In addition to their fast dissolution in water (saliva) and absorption from the oral cavity, they can enter the systemic blood circulation without undergoing first pass effect (30, 31). Therefore, they may have higher bioavailability, a lower \( T_{\text{max}} \) and a higher \( C_{\text{max}} \) (20, 32). Other advantages include availability in a variety of shapes and sizes, not leaving a residue in mouth, and having acceptable taste (33).

3.2. Disadvantages of Fast Dissolving Systems

Although the hygroscopicity is preferred for fast dissolving of the drugs, it is also the most important drawback of these systems (7), which need special requirements such as packaging. Furthermore, particular dosage forms may have their own disadvantages including choking for tablets and inefficiency for high drug loading in films and nanofibers (13, 32). Released drug from fast dissolving dosage form in the mouth has a strong contact with taste buds on the tongue, this could be challenging for drugs with bitter taste (17, 33-35), which needs taste masking techniques.

3.3. Formulation Ingredients

Depending on the type of fast dissolving system that is to be manufactured, different ingredients are used. They are more or less the same in different dosage forms and will be explained briefly (35-38). It should be noted that not all ingredients are common for all types of FDS (28, 29).

3.3.1. General Ingredients

3.3.1.1. Active Pharmaceutical Ingredient (API)

Several drugs of different pharmacological classes are used to prepare fast dissolving systems including analgesics such as acetaminophen and caffeine (28), indomethacin (39), ibuprofen (40) and diclofenac (41, 42), anti-migraines such as donepezil (43, 44) and sumatriptan (12, 45), anti-emetics such as metoclopramide and dimenhydrinate, antibiotics (46) and miscellaneous categories (15, 31, 33, 47, 48).

3.3.1.2. Saliva Stimulating Agents

Since FDS are supposed to be used without water, they need to be dissolved in saliva; hence, to increase the rate of dissolution, the saliva stimulating agents can be used in some formulations. However drugs such as ascorbic acid and nicotinamide can stimulate the excretion of saliva by itself (4, 49).

3.3.1.3. Flavoring Agents

Most drugs have bitter taste and because these dosage forms are absorbed through the oral cavity, contact with taste buds is very likely. Flavoring agents are added to mask the bitter taste of drugs (50).

3.3.1.4. Coloring Agent

Some drugs and excipients have different shades of color and a non-uniform appearance is not attractive for the patients. Therefore, coloring agents and opacifiers are used to maintain a uniform color and appearance (51, 52).

3.3.1.5. Surfactants

In FDS formulations with some insoluble or poorly soluble ingredients, an appropriate surfactant may be used to improve the dissolution rate of the drug (53-55).

3.3.2. Specific Ingredients

In addition to general ingredients that can be used for all FDS, each system could have its own specific ingredients that are mentioned in Table 1 and explained briefly.

3.3.2.1. Polymers

Are among the most important excipients used in FDS. Interaction between API and polymer determines the amount of loading and rate of dissolution. Hydrophilic natural or synthetic polymers can be used to prepare fast dissolving films or strips (61-65). Some of the common polymers used to manufacture films or nanofibers are poly (lactide-glycolide) (40, 66), chitosan (67, 68), collagen (69), poly (lactide-caprolactone) (70, 71), cellulose acetate phthalate, polyvinyl alcohol (53, 72, 73), polyethylene glycol, polyvinyl pyrrolidone (12, 27, 47, 74-77) and cellulose derivatives such as hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC) (48).

3.3.2.2. Plasticizers

They are used to improve the film’s mechanical strength and prevent breaking due to fragility (63, 78, 79).

3.3.2.3. Super Disintegrants

These excipients including microcrystalline cellulose, hydroxypropyl methyl cellulose, modified starch, crospovidone and croscarmellose are used in a concentration of 5-10% to ensure rapid disintegration of tablets in order to enhance dissolution rate and quick absorption of drug. Super disintegrants do their function through different mechanisms; they can swell in contact with water or improve the absorption of water into the dosage form (80-84).

3.3.2.4. Binders

Also called as adhesives, are added to the tablet formulation to ensure the required strength to compact the powder, and is used in very low amounts (1% - 2%) (58, 85).
3.3.2.5. Lubricants
Lubricants are used to lower the friction and adhesion between the tablet surface and die during tablet ejection (86, 87). Although, it should be noted that hydrophobic lubricants such as calcium or magnesium stearate may delay the disintegration of the fast dissolving tablet; hence it is suggested to use hydrophilic lubricants such as sodium or potassium benzoate for these dosage forms (88).

3.3.2.6. Fillers
Filler is 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, (59).

3.4. Preparation Methods of FDS
Preparation of different FDS dosage forms vary from each other. The methods are shown in Table 2 and each method is then explained briefly. It should be noted that only some of these methods are commercialized for FDS preparation and other techniques are mostly used in researches.

3.4.1. Tablet Preparation

3.4.1.1. Lyophilization
The process of drying at low temperature by sublimation technique gives the tablets a highly porous structure. It is also useful for heat sensitive drugs (48, 93-95).

3.4.1.2. Spray Drying
An aqueous solution containing the drug, a specific matrix and other excipients is sprayed to make a fine powder by vaporizing the solvent. The resulted fine particles are then compressed into tablets (96).

3.4.1.3. Molding
It contains preparation of a suspension or moist powder followed by compression and drying in molded plates, giving the tablet a less compact and porous structure (97, 98).

3.4.1.4. Sublimation
Is a technique to remove subliming material by sublimation from the compressed tablets giving it high porosity and rapid dissolution in saliva (37, 95-98).

3.4.1.5. Mass Extrusion
In this technique the ingredients are blended together, making a moist mixture, then driven out through the extruder to form cylindrical extrudates which can be cut into tablets (99).

3.4.1.6. Direct Compression
It is a fast and simple technique in tablet manufacturing. The powder blend is compressed by the tableting machine to form tablets in different sizes and shapes without the need to granulation process (100-103). This technique may be the final stage of other methods to prepare tablets.

3.4.2. Film Preparation

3.4.2.1. Solvent Casting
In this technique the drug and all of the water soluble excipients are dissolved in a solvent to form a homogeneous viscous solution which is then poured into a plate and dried. In some cases the water soluble and water insoluble ingredients can be dissolved in specific solvents separately and then the two solutions can be mixed (6, 104, 105). Fast dissolving films of maltodextrin and verapamil (4, 106) and fast dissolving films of meclizine (107) were made by this technique.

3.4.2.2. Semi-Solid Casting
A plasticizer and an acid insoluble polymer solution are added to a solution of water soluble polymer, thus forming a gel which is casted into films by heat controlled drums (34, 62, 104).

3.4.2.3. Hot Melt Extrusion
It is the process of applying heat and pressure to a molten polymer and extruding it through an orifice in a continuous process. This process is mostly used to make granules, tablets, transdermal and transmucosal delivery systems (36, 108, 109). The method is used to make fast dissolving films of maltodextrin (4).

3.4.2.4. Rolling
Two premix solutions containing a film forming polymer, a polar solvent and other excipients are made. API is added to one solution, and then all the solutions are poured into the feed tank and mixed together. After that, the mixed solution is carried away by a roller and dried to form a film using bottom drying (34, 62).

3.4.2.5. Solid Dispersion
The drug and hydrophilic polymers are dissolved or dispersed in a solvent and left to dry in the shape of films. The resulted films consist of an amorphous carrier which its drug molecules or particles are dispersed homogeneously in the matrix. This method is used to make fast dissolving acetaminophen films (110-114).

3.4.2.6. Compaction
The method is commonly used as a dry granulation technique in the pharmaceutical industry to produce tablets with ingredients sensitive to heat and moisture. This method is mostly used to make matrix films from two different polymers (115, 116).
3.4.3. Nanofiber Preparation

There are different methods to prepare nanofibers (Table 2). However the electrospinning technique is a promising method to prepare nanofibers in research and industry. Nanofibers prepared by electrospinning are the most suitable choices to improve dissolution and hence bioavailability of drugs and the method has gained attention due to its efficacy and advantages over traditional preparation technologies (39, 117). The following part focuses on this method of preparation (28, 29, 69).

3.4.3.1. Electrospinning Method

In the electrospinning process, a high voltage power supply (118) is used to provide a desirable voltage between the solution and the collector (28, 119). Spinning solutions are carefully loaded into a syringe attached to a stainless steel capillary metal-hub needle (28) and the specific feed rate of the solution is maintained to avoid air bubbles. The positive electrode of the high voltage power supply is connected to the needle tip (117). The earthed electrode is connected to a metal collector (29). Collectors have different sizes and shapes due to their application. Increasing the voltage between the two electrodes induces a tailor cone formation at the tip of the needle and at a specific voltage (89), depending on the concentration and type of polymer, the solution exits the needle tip as a fiber jet and is shot toward the collector (28), thinning of the fibers to nanosize and drying by solvent evaporation take place on the way to the collector (118-120). Sometimes the melted polymer solutions can be used and the film is solidified by cooling on the way to the collector (39, 121, 122). The distance between the needle tip and collector, the voltage and the feed rate of the syringe have to be adjusted to obtain a suitable fiber jet and proper nanofibers (43, 118). Electrospun nanofibers are usually collected as a film or strip and can be developed in various sizes and shapes according to their administration (39, 117, 122).

3.5. Special Advantages of Electrospun Nanofibers

Electrospinning process is preferred to prepare nanofibers due to its efficiency and simplicity in fabrication, versatility in manufacturing different drugs and polymers, low cost of production and possibility to scale up to the industrial level (121, 123).

Electrospun nanofibers have a large surface area that leads to fast dissolution and/or disintegration of the film (85). These nanofiber films have merged the stability of solid dosage forms with the bioavailability of liquid forms because of high surface area to volume ratio (118) which enhances fast dissolution and high solubility. A very useful advantage is the ability to be manufactured using just an API and polymer (111, 124), thus reducing any side effects of excipients and lowering the cost of production. For the process of electrospinning, crystallized or amorphous drugs can be used, but researches show that even crystallized drugs turn into amorphous state through the electrospinning process, because of fast solvent evaporation which gives the drug no time to crystal growth and making them more likely to dissolve rapidly (39, 120).

In addition to the benefits of electrospinning, nanofibers prepared by this technique also have some specific advantages. Drugs in the nanofiber structures have a faster permeation rate across oral mucosa (117). They can also be used to treat localized conditions in oral cavity due to their mucoadhesive property (125) as well as systemic absorption (28, 29). Encapsulating drugs as nanofibers enhances the bioavailability of drugs due to faster disintegration and dissolution (45, 126, 127). Furthermore, insoluble or swellable polymers are used in nanofibers to control the drug release (42, 120). Using other drug delivery systems such as nanoparticles or microemulsions in combination with nanofibers are also under study (70, 119).

3.6. Evaluation of Fast Dissolving Systems

Although the evaluation techniques for tablets are different from films and nanofibers, the main ideas are the same. However explaining all of the evaluation methods is far from the scope of this review, they are only mentioned briefly in Table 3 (32, 34, 36, 45, 47).

The FDS evaluation tests in some cases need special conditions or modifications compared to the traditional dosage forms; for example due to the fast dissolution and disintegration of FDS, the test procedures should be filmed by a high speed camera to make it possible to determine the time of dissolution and disintegration. Also for films and nanofibers, a low volume media are used for dissolution test (5 - 10 mL). Table 4 shows the dissolution and disintegration time for different FDS dosage forms (28, 29, 42).

Table 1. Specific Ingredients of Different Fast Dissolving Systems Dosage Forms

| Fast Dissolving Tablets (35, 37, 56-59) | Fast Dissolving Films (36, 60) | Fast Dissolving Nanofibers (1, 29) |
|-------------------------------------|-------------------------------|-----------------------------------|
| Super disintegrant                  | Polymer                        | Polymer                           |
| Binder                              | Plasticizer                    | -                                 |
| Lubricant                           | -                              | -                                 |
| Filler                              | -                              | -                                 |

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Table 2. Preparation Methods of Different Fast Dissolving Systems Dosage Forms

| Tablets (35, 37, 56, 59) | Films (32, 36, 60, 61) | Nanofibers (29, 89-92) |
|-------------------------|------------------------|------------------------|
| 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 |

Table 3. Evaluation Methods of Fast Dissolving Systems

| Tablets | Films and Nanofibers |
|---------|----------------------|
| Taste/ Mouth sensation | Morphology study (31) |
| Tablet thickness | Organoleptic evaluation |
| Taste/ mouth sensation | Thickness |
| Tablet thickness | Mechanical properties |
| Hardness | Tensile strength |
| Crushing strength | Tear resistance |
| | Elastic modulus |
| | Percentage elongation |
| | Folding endurance |
| Water absorption ratio | Swelling property |
| Disintegration time (47) | Disintegration time |
| Dissolution test (31, 128) | Dissolution test (110) |
| Wetting time | |
| Friability | Fiber diameter (only for nanofibers) (3, 29, 89) |
| Uniformity of dispersion | |

Table 4. Disintegration and Dissolution Time of Fast Dissolving Systems Dosage Forms

| Dosage Form | Fast Dissolving Tablets (30, 37, 85, 129) | Films (4, 64, 129, 130) | Nanofibers (28, 29, 111, 112) |
|-------------|------------------------------------------|--------------------------|-------------------------------|
| Dissolution time, s | < 180 | < 60 | < 150 |
| Disintegration time, s | < 180 | < 38 | < 1 |

4. Conclusions

Nowadays, patients are looking for rapid effect of medications (40, 45) and due to the difficulties and bad compliance of injectable dosage forms, they prefer to use rapid acting oral dosage forms (27). Oral fast delivery systems are the most convenient forms for fast drug delivery (3, 39). They are available in different types of dosage forms (47), and are developing in order to improve effectiveness, feasibility, ease of production and administration (111). As shown in Table 4, nanofibers have the fastest dissolution time among different fast dissolving systems, which is due to their very high porosity (28, 29).

Thus they can be used as novel drug delivery systems for fast dissolving purposes (131).

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Footnote
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critical revision, and Maryam Kouchak and Pooria Taghavi Moghadam participated in revising the manuscript.

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