
Fast Dissolving Drug Delivery Systems: A Review of the Literature

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Recently, fast-dissolving 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. Usually, elderly people experience difficulty in swallowing the conventional dosage forms (tablets, capsules, solutions and suspensions) because of tremors of extremities and dysphagia. Fast-dissolving drug delivery systems may offer a solution for these problems. Fast dissolving drug delivery can be achieved by various techniques like direct compression, wet granulation, compression moulding, volatilization and freeze-drying. They involve different mechanisms like use of high amounts of hydrophilic disintegrating agents of effervescent combinations, which allow the dosage forms to disintegrate quickly in the patient's mouth on contact with saliva. There are more than fifteen fast-dissolving products in the market worldwide.

Among the pharmaceutical dosage forms, the conventional tablet seems to be most popular, because of its ease of transportability and comparatively lower manufacturing cost. However, for the elderly and the infants, conventional tablets present certain difficulties while consuming and liquid dosage forms are preferred. Fast dissolving tablets have the advantages of both solid and liquid dosage forms¹. A sizeable section of the pharmaceutical research is focussed on the development of these fast dissolving delivery systems. A fast dissolving system can be defined as a dosage form for oral administration, which when placed in mouth, disintegrates rapidly or dissolves and can be swallowed in the form of a liquid².

Advantages of the fast dissolving dosage form:

1. Ease of administration for patients who are mentally ill, disabled and uncooperative.
2. Requires no water intake.
3. Quick disintegration and dissolution of the dosage form.
4. Overcomes unacceptable taste of the drugs.
5. Can be designed to leave minimal or no residue in the

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mouth after administration and also to provide a pleasant mouth feel.

6. Allows high drug loading.

CHARACTERISTICS OF FAST DISSOLVING DELIVERY SYSTEMS

Taste of the medicament:

As most drugs are unpalatable, mouth dissolving delivery systems usually contain the medicament in a taste masked form. Delivery systems dissolve or disintegrate in patient's mouth, thus releasing the active ingredients which come in contact with the taste buds and hence, taste masking of the drugs becomes critical to patient compliance.

Hygroscopicity:

Several fast dissolving dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence they need protection from humidity which calls for specialized product packaging².

Friability:

In order to allow fast dissolving tablets to dissolve in

the mouth, they are made of either very porous and soft-moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle which are difficult to handle, often requiring specialized peel-off blister packing. To overcome this problem, some companies introduced more robust forms of fast dissolving tablets, such as Wowtab[®] by Yamanouchi-Shaklee and DuraSolv[®] by CIMA labs³.

CONVENTIONAL TECHNIQUES USED IN THE PREPARATION OF FAST DISSOLVING DRUG DELIVERY SYSTEMS

Tablet moulding:

In this method, the delivery system is prepared in the form of tablets using water-soluble additives, to allow the tablets to dissolve rapidly and completely in mouth. All ingredients of the formulation are passed through fine mesh, dry blended, wetted with a hydro-alcoholic solvent and then compressed into tablets using low compression forces. The solvent present inside the tablets is removed by air-drying. The so formed moulded tablets contain a porous structure, which enhances dissolution. The moulded tablets prepared by above method possess low mechanical strength. To improve the mechanical strength, a binding agent like sucrose, polyvinyl pyrrolidone, cellulosic polymers like hydroxypropyl methylcellulose may be added to the solvent system³.

The scope for taste-masking in moulded tablets is very limited. To mask the unpalatable taste of medicaments, Van Scoik⁴ had developed a particulate drug matrix by congealing a molten mixture of hydrogenated cotton seed oil, lecithin, polyethylene glycol, sodium bicarbonate and drug and incorporated the same into a lactose-based triturate form to produce taste masked mouth dissolving tablets. Masaki⁵ prepared intrabuccally fast-disintegrating tablets using agar solution as binder and moulding the preparation into a blister pack. In this process, a suspension containing an active ingredient, agar and soluble sugars like lactose and/or mannitol is prepared and filled into the blister packaging well, solidifying the preparation into a jelly form at room temperature, and dried at 30° under a pressure of 700 to 760 mm. Hg. The moulded tablets obtained by this method would have adequate strength with hardness greater than 2.0 kg/cm².

In another process, the drug containing microparticles are combined with an effervescent disintegrating agent, which on dissolution forms a tasteless drug suspension in the mouth⁶. Although prompt release is preferred, the protective material utilized in the microparticle should not dissolve instantaneously in water or saliva. That is, the

microparticle should resist dissolution and release for a period of time, typically a few seconds or so, sufficient to permit the patient to swallow the released microcapsules as the tablet disintegrates. A combination of polymers (cellulose and synthetic cellulose derivatives, Eudragit. RL30-D) along with release promoters like soluble sugar (mannitol and magnesium oxide) serves the purpose. The size of microparticles may preferably be between 150 to 500 μm (100 mesh to 35 mesh). The microparticles are then blended with effervescent disintegrant and other adjuvants like binder, diluent, lubricant, color and flavour, and granulated by compaction, extrusion or globulation, and compressed into tablets.

Fast-disintegrating tablets prepared by vacuum drying process are reported by Pebley *et al.*⁷ In this method, a frozen mixture containing a gum (e.g. guar, tragacanth, carrageenan or xanthan gum), carbohydrates (e.g. mannitol, dextrose, maltose, sucrose or corn syrup), and a solvent was vacuum dried in a tablet shaped mould, which resulted in tablets with enhanced structural integrity than traditional moulded tablets.

Spray drying:

Spray drying is a process by which highly porous, fine powders can be produced. Allen and Wang^{8,9}, Allen *et al.*^{10,11}, reported a spray drying technique for preparing fast-dissolving tablets. The composition contained a bulking agent (e.g. mannitol and lactose), a disintegrant (e.g. sodium starch glycollate and croscarmellose sodium), an acidic ingredient (citric acid) and/or alkali ingredients (e.g. sodium bicarbonate) which when compressed into tablets showed fast disintegration and enhanced dissolution.

Lyophilization:

Lyophilization is a pharmaceutical manufacturing technology which allows drying of heat sensitive drugs and biologicals at low temperatures under conditions that allow removal of water by sublimation¹². Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability. Jaccard and Leyder¹³ employed lyophilization technique in making one oral pharmaceutical preparation and found increased absorption and bioavailability of spironolactone, nicergoline and troleandomycin in comparison to their conventional formulation. Remon and Corveleyn¹⁴ in one of their study found maltodextrins very useful in preparing fast-dissolving tablets by lyophilization technique. Tablets prepared by lyo-

philization, are fragile and possess low mechanical strength, which make them difficult to handle and they also exhibit poor stability on storage under stressed conditions. Blank *et al.*¹⁵ used a mixture of mannitol and one natural gum (e.g. acacia, guar or xanthan gum) as a carrier material, in formulation of lyophilized fast-dissolving tablets and found good stability in blister pack even when stored at high humidity conditions. Water penetrates through pores of network, resulting in rapid disintegration and / or dissolution of the dosage form.

Sublimation:

Roser and Blair¹⁶ described a method of preparing highly porous and rapidly dissolving tablets, which includes the addition of a sublime salt to the tableting components, compressing the blend and removing the salt by the process of sublimation. The active ingredient, a diluent (e.g. lactose and trehalose), a sublime salt (e.g. ammonium carbonate, ammonium bicarbonate and ammonium acetate), a binder and other excipients are blended and tablets are prepared. Then volatile salt is removed by sublimation, by exposing the tablet to reduced atmospheric pressure for a time sufficient to completely remove the salt.

Koizumi *et al.*¹⁷ prepared fast dissolving, highly porous compressed tablets by sublimation technique. Mannitol is incorporated as diluent and camphor as sublime material. Tablets prepared by this method dissolve rapidly (20 s) and possess sufficient hardness. Water can also be used as pore forming material for preparation of highly porous fast dissolving tablets. A mixture of active ingredient and a carbohydrate (e.g. sucrose, glucose, xylitol or mannitol) was wetted with suitable amount of water and compressed into tablets. The water is evaporated, producing highly porous tablets with good mechanical strength¹⁸.

Addition of disintegrants:

Addition of disintegrants in fast dissolving tablets, leads to quick disintegration of tablets and hence improves dissolution. Microcrystalline cellulose, cross linked carboxymethyl cellulose sodium, cross linked polyvinyl pyrrolidone and partially substituted hydroxypropyl cellulose, though water insoluble, absorb water and swell due to capillary action and are considered as effective disintegrants in the preparation of first dissolving tablets. Watanabe and Kayano⁹ prepared quick disintegrating tablets using microcrystalline cellulose and low substituted hydroxypropyl cellulose as disintegrants and found fast disintegration in ratios of 8:2-9:1, and the resultant tablets showed good mechanical strength. Ito and

Sugihara²⁰ used agar powder as disintegrant in developing fast disintegrating tablets. Upon contact with water, agar powder absorbs water and swells without becoming gelatinous at ordinary temperatures. Tablets prepared with agar powder showed good hardness and quick disintegration. Fast disintegration of tablets can also be achieved by incorporating effervescent disintegrating agents, which generate carbon dioxide. This phenomenon also resulted in partial taste-masking of unacceptable taste of the drug²¹. EFVDAS is an effervescent drug delivery system used by Elan in the development of pharmaceutical products (e.g. paracetamol, ibuprofen, cimetidine, and naproxen).

Taste masking:

Taste masking is an essential requirement for fast dissolving tablets for commercial success. Taste masking of the active ingredients can be achieved by various techniques: Drugs with unacceptable bitter taste can be microencapsulated into pH sensitive acrylic polymers²². Cefuroxime axetil is microencapsulated in various types of acrylic polymers (e.g. Eudragit E, Eudragit L-55 and Eudragit RL) by solvent evaporation and solvent extraction techniques. These polymer microspheres showed efficient taste masking and complete dissolution in a short period. Fine granules of drug and disintegrant (e.g. low substituted hydroxypropyl cellulose) when coated with a water insoluble polymer (e.g. ethylcellulose) masked the bitter taste of sparfloxacin²³. The addition of low substituted hydroxypropyl cellulose as disintegrant to the drug in cores, resulted in increased dissolution rate and bioavailability of sparfloxacin compared to its conventional tablets²⁴.

A novel microencapsulation process combined with wet spherical agglomeration technique was also developed by using a modified phase separation method to mask the bitter taste of the drugs²⁵. The spherical agglomerates containing enoxacin and other additives including disintegrants were produced in acetone-n-hexane-ammonia water or acetone-n-hexane-distilled water system by wet spherical agglomeration, applying the phenomena of flocculation of particles in liquid. The agglomerates obtained could be microencapsulated with Eudragit RS by phase separation technique. The resulting microcapsules were free from bitter taste and were found bioequivalent to the commercial enoxacin tablets.

A polymer carrier system developed by Lu *et al.*²⁶ was used to reduce the bitter taste of macrolides (e.g. erythromycin and clarithromycin) by complexation to carbopol. The ionic bonding of amine macrolide to the high molecular

weight polyacrylic acid results in macrolide-carbopol complex with reduced bitter taste. These complexes are prepared by dissolving or dispersing the drug and polymer in water or hydro-alcoholic mixtures. Further taste masking of the complex is achieved with polymer coatings (e.g. hydroxypropyl methylcellulose phthalate (HP-55)) despite which it exhibits good bioavailability.

Ozer and Hincal²⁷ reported a simple coacervation method using gelatin, and anhydrous sodium sulphate as coacervating agent for taste masking of beclamide. Beclamide is an anti-epileptic drug with unpleasant taste. It is microencapsulated into gelatin, with sodium sulphate as coacervating agent, and glutaraldehyde as hardening agent. The microcapsules after formation are dehydrated using alcohol. The core: wall substance ratio was 1:1, and the taste could be successfully masked.

Microparticles of drug coated with a mixture of hydrogenated oil and surfactants in fluidized air bed using side spray method and heat-treating the coated particles at a temperature above the melting point of the surfactant, resulted in taste masking and enhanced dissolution of indeloxazine hydrochloride²⁸.

A novel technique for taste masking of macrolides (e.g. erythromycin and clarithromycin) is reported by Yajima *et al.*²⁹. Monoglycerides having a low melting point which can form good elaborate film, and easily soluble in intestine, and polymers which are insoluble in the mouth (pH 5-8), but are freely soluble in stomach (pH 1-4), are selected for taste masking of drugs with unpleasant taste. The polymer is dissolved or dispersed in monoglyceride, and the drug is granulated with above mixture and the resultant granules are cooled.

PATENTED TECHNOLOGIES OF FAST DISSOLVING DRUG DELIVERY SYSTEM

ZYDIS

Using the concept of Gregory *et al.*³⁰ Scherer has patented the Zydys technology. Using the freeze drying process, this technology converts the mixture of active ingredient and water dispersible carrier materials into open matrix network that disintegrates rapidly. The network is highly porous solid foam which allows rapid penetration of liquid and facilitates quick disintegration of the dosage unit. In Zydys technology, drug is added to a solution of carrier material (preferably gelatin) to obtain dispersion, and the dispersion is filled into preformed pockets of blister pack by automatic means, and freeze dried to produce the final dosage form. The blister

pack containing the dosage form are sealed with peelable backing foil, because the units formed are very fragile and do not possess good mechanical strength. The dosage form is highly moisture sensitive and hence, needs packing into additional moisture proof foil. The amount of drug that could be incorporated should generally be less than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. The particle size of the insoluble drugs should be less than 50 μm and not more than 200 μm to prevent sedimentation during processing³¹. Most compounds in a Zydys formulation are claimed to be bioequivalent to their respective existing solid oral dosage forms.

ORASOLV

CIMA labs has developed OraSolv technology. The system essentially makes tablets that contain the taste masked active ingredients and an effervescent disintegrating agent, which on contact with saliva, rapidly disintegrates and releases the taste masked active ingredient. The tablets are made by direct compression at very low compression forces in order to minimize oral dissolution time. Conventional blenders and tablet presses are used to produce the tablets. The tablets produced are soft and friable and are packaged in specially designed pick-and-place system. PaksolvTM, a proprietary packaging system consisting of specialized tablet transfer, packaging equipment, and unique packaging materials and designs, is developed by CIMA labs to pack the soft, friable tablets, to protect it from attrition and breakage during transportation. CIMA has carried out an internal study comparing an OraSolv famotidine tablet with a conventional famotidine tablet (Pepcid[®]). The plasma profiles of both the formulations were comparable and the additional taste masking of drug in OraSolv formulation does not alter the absorption kinetics of famotidine². There are six OraSolv formulations marketed worldwide. These formulations can accommodate single or multiple active ingredients, and tablets containing more than 1.0 g of drug have been developed. Their disintegration time is less than 30 s. The OraSolv formulations are not very hygroscopic.

DURASOLV

DuraSolv is another fast dissolving technology patented by CIMA labs. The tablets made by this technology consist of a drug, fillers and a lubricant. DuraSolv tablets are prepared by using conventional tableting equipment and have good rigidity (friability less than 2%). They can be packaged into conventional packaging systems like blisters, pouches or bottles. DuraSolv is an appropriate technology for products requiring low amounts of active ingredients.

FLASH DOSE

Fuisz has patented the flash dose technology. Nurofen meltlets, a new form of ibuprofen as melt-in-the-mouth tablets, prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consists of self-binding shearform matrix termed as "floss". Shearform matrices are prepared by flash heat processing and are of two types.

- a) Single floss or Unifloss, consisting of a carrier, and two or more sugar alcohols, of which one is xylitol.
- b) Dual floss consists of a first shearform carrier material (termed "base floss", contains a carrier and at least one sugar alcohol generally sorbitol), and a second shearform binder matrix ("binder floss"; contains a carrier and xylitol).

In flash heat process, the feed stock (carbohydrates including sugars and polysaccharides) is simultaneously subjected to centrifugal force and to a temperature gradient, resulting in discrete fibers. The preformed matrices obtained are partially crystallized and have good self-binding and flow properties. Crystallization can be performed by using crystallization enhancers (e.g. ethanol, polyvinyl pyrrolidone, water and radiant energy) at a concentration of about 10% and crystallization modifiers (e.g. surfactants which include, lecithin, propylene glycol, spans, tweens and polyethylene glycol) upto 10% by weight of tablet composition. The so formed matrices are complex crystalline structures with high specific surface area and result in rapid dissolution rate of the drug. The shearform matrix is blended with drug (usually taste masked) and other tableting ingredients, and compressed into tablets using conventional tableting equipment³¹. The tablets produced, dissolve rapidly in the saliva of mouth. Flash dose tablets are soft, friable and hygroscopic dosage forms, which require specialized packaging.

WOWTAB

Wowtab technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water". This process uses a combination of low mouldability saccharide (rapid dissolution) and high mouldability saccharide (good binding property) to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide (e.g. lactose, glucose, sucrose, mannitol and xylitol) and granulated with a high mouldability saccharide (e.g. maltose, sorbitol and oligosaccharide) and compressed into tablets³².

The ratio of high mouldability saccharide to low mouldability saccharide used is 2 to 20% by weight. In other process, the low mouldability saccharide is granulated with high mouldability saccharide, and the resultant granules are mixed with active ingredient and subjected to compression using conventional tableting equipment. The active ingredients may be used in amounts of 50% w/w or less, preferably 20% w/w of the tablet.

FLASHTAB

Prographarm laboratories has patented the flashtab technology³³. This technology involves the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, microencapsulation, extrusion-spheronization or simple pan coating method. The microcrystals or microgranules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation, and compressed into tablets. All the processing utilized the conventional tableting technology, and the tablets produced are reported to have good mechanical strength and disintegration time less than one minute.

CONCLUSION

The introduction of rapidly disintegrating dosage forms has solved some of the problems encountered in administration of drugs to the pediatric and elderly patient. Most of the techniques used to produce this dosage form require conventional tableting equipment. Keeping in view of the advantages of the delivery system, rapidly disintegrating dosage forms have been successfully commercialized, and because of increased patient demand, these dosage forms are expected to become more popular.

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