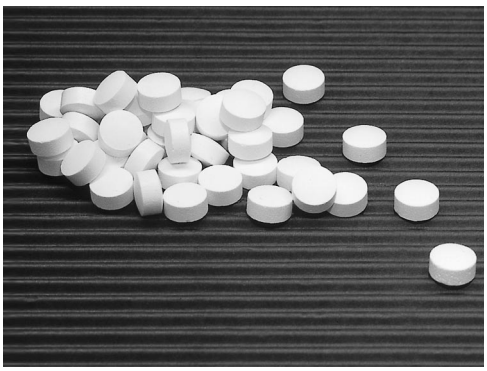
Fast-Melting Tablets: Developments and Technologies

Luca Dobetti



MIKE DEAN

The demand for fast-melting tablets (FMTs) has been growing during the last decade, particularly for children and the elderly who have difficulty swallowing tablets and capsules. These dosage forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then swallowed without the need for water. The advantage of this convenient administration has encouraged both academia and industry to generate new fast-disintegrating formulations and technological approaches in this field. This article reviews the latest progress in the development of FMTs. (This article was published previously in *Pharmaceutical Technology Europe* 12 [9], 32–42 [2000].)

Luca Dobetti is the R&D manager at Eurand International SpA, Site of Trieste, Via del Follatoio 12, I-34100 Trieste, Italy, tel. +39 040 899 2242, fax +39 040 899 2243, e-mail ldobetti@eurand.it

Many patients have difficulty swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy (1). The demand for solid dosage forms that can be dissolved and suspended in water, chewed, or rapidly dissolved in the mouth is particularly strong in the paediatric and geriatric markets, with further application to other patients who prefer the convenience of a readily administered dosage form.

Because of the increase in the average human life span and the decline, with age, in swallowing ability, oral tablet administration to patients is a significant problem and has become the object of public attention (2,3). The problem can be resolved by the creation of rapidly dispersing or dissolving oral forms, which do not require water to aid swallowing. The dosage forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way. Less frequently, they are designed to be absorbed through the buccal and oesophageal mucosa as the saliva passes into the stomach. In the latter case, the bioavailability of a drug from fast-dispersing formulations may be even greater than that observed for standard dosage forms. Furthermore, side effects may be reduced if they are caused by first-pass metabolites (1,4).

Fast-dispersing formulations, commonly called fast-melting tablets (FMTs), also offer advantages over other dosage forms such as effervescent tablets, extemporary suspensions, chewing gum, or chewable tablets, which are commonly used to enhance patient compliance. Effervescent tablets and extemporary suspensions require preparatory steps before administration of the drug. The elderly, who often are unable to chew large pieces of gum or tablets, sometimes experience unpleasant taste problems when bitter drugs are present. In this case, the bitterness of the chewable tablets markedly increases because of the prolonged time that they are in the mouth or as a result of leaching of the drug from chewed or broken microcapsules.

The advantages of FMTs increasingly are being recognized in both industry and academia. Their growing importance was underlined recently when the European Pharmacopoeia adopted the term *orodispersible tablet* as a "tablet to be placed in the mouth where it disperses rapidly before swallowing" (5).

Technologies

Three general technologies, detailed below and summarized in Table I, are commonly applied for the production of fast-disintegrating systems. They are

- freeze-drying
- moulding (compression or heat-moulding)
- direct compression.

Freeze-drying. Freeze-drying (lyophilization) is a process in which water is sublimated from the product after freezing. The main advantage being that pharmaceutical substances can be processed at non-elevated temperatures, thereby eliminating adverse thermal effects, and stored in a dry state with relatively few shelf-life stability problems. Freeze-dried forms offer more-rapid dissolution times than other available solid products. The lyophiliza-

tion process imparts a glassy amorphous structure to the bulking agents and, sometimes, to the drug, thereby enhancing the dissolution characteristics of the formulation.

The use of freeze-drying, however, is strongly limited by the time and handling required for processing, the limited amount of materials processed for each batch, and the high cost of the equipment and processing. Other major disadvantages of the final dosage forms include the lack of physical resistance in standard blister packs and their limi-ted ability to accommodate adequate concentrations of active.

Table I: Summary of the advantages and disadvantages of the different technologies for preparing rapidly disintegrating pharmaceutical forms.

Technology	Advantages	Disadvantages
Ziplets	Low cost of production	Not applicable to water-soluble compounds
	Use of standard equipment/materials	
	Very good physical resistance	
Freeze-drying	Immediate dissolution (<5 s)	Very poor physical resistance
		High cost of production
		Low dose of water-soluble drugs
Moulding	Very rapid dissolution (5–15 s)	High cost of production
	High dose	Weak mechanical strength
		Possible limitations in stability
Tabletting (standard)	Low cost of production	Disintegration capacity markedly limited by the size and hardness of the tablets
	Use of standard equipment/materials	
	High dose	
	Good physical resistance	
Tabletting (effervescent)	Use of standard equipment	Operating in controlled low humidity
	High dose	Need of totally impermeable blister
	Good physical resistance	
	Pleasant effervescent mouth feel	

Examples of an FMT obtained by freeze-drying technology. R.P. Scherer's (Basking Ridge, NJ) Zydis formulations consist of a drug physically trapped in a water-soluble matrix, which is freeze-dried to produce a product that dissolves rapidly when placed in the mouth (1,4). The matrix consists of a water-soluble mixture of saccharide and polymer, formulated to provide rapid dispersion properties and to allow sufficient physical strength to withstand handling during use. Because of Zydis's weak physical strength, the unit is contained in a peelable blister pack, which allows removal of the product without damaging it.

The ideal drug candidate for Zydis would be chemically stable and water-insoluble, and have a small particle size (preferably lower than 50 µm) (1,4). Water-soluble drugs might form eutectic mixtures and not freeze adequately; consequently, the dose is usually limited to 60 mg. Larger drug-particle sizes might present sedimentation problems during manufacture (1).

Lyoc (Farmalyoc; Laboratoire L. Lefon, Maisons-Alfort, France) is a porous, solid galenic form obtained by lyophilization of an oil-in-water emulsion placed directly in the blister alveolus (6,7). Lyoc's unusual properties result from the preparation method — freezing a thickened (paste-like) emulsion containing the active as bulk or in coated microparticles. The final product, which accommodates high drug dosing, disintegrates rapidly but possesses poor mechanical resistance.

Quicksolv (Janssen Pharmaceutica, Beerse, Belgium) is a porous solid form obtained by freezing an aqueous dispersion or solution of the active-containing matrix, then drying the matrix by removing the water using an excess of alcohol (solvent extraction) (8). The final form disintegrates very rapidly but is limited to low drug content and can be used only with those actives that are insoluble in the extraction solvent.

Moulding. Moulded tablets usually are prepared from soluble ingredients by compressing a powder mixture previously moistened with solvent (usually ethanol or water) into mould plates to form a wetted mass (compression moulding). Recently, moulded forms also have been prepared directly from a molten matrix in which the drug is dissolved or dispersed (heat moulding) or by evaporating the solvent from a drug solution or suspension at standard pressure (no-vacuum lyophilization).

Tablets produced by moulding are solid dispersions. The physical form of the drug in the tablets depends on whether, and to what extent, it dissolves in the molten carrier. The drug can exist as discrete particles or microparticles dispersed in the matrix. It can dissolve totally in the molten carrier to form a solid solution, or dissolve partially in the molten carrier while the remaining particles stay undissolved and dispersed in the matrix. The characteristics of the tablets (such as disintegration time, drug dissolution rate, and mouth feel) will depend on the type of the dispersion or dissolution.

Because the dispersion matrix is, in general, made from water-soluble sugars, moulded tablets disintegrate more rapidly and offer improved taste. These properties are enhanced when tablets with porous structures are produced or when components that are physically modified by the moulding process are used. Unfortunately, moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablets often occurs during tablet handling and when blister pockets are opened. Hardness agents can be added to the formulation, but then the rate of tablet solubility usually decreases.

FMTs, having both adequate mechanical strength and good disintegration, recently have been prepared by moulding techniques using nonconventional equipment and/or multistep processes. The nonconventional approach, however, does cost more. Compared with freeze-drying, FMTs prepared by moulding techniques can be produced more simply and efficiently at an industrial scale, although they cannot achieve disintegration times comparable with those of lyophilized forms.

Flashdose (Fuisz Technologies Ltd, Chantilly, VA) is a rapidly dissolving tablet manufactured using a candy floss or shearform matrix (9,10). The matrix is formed from saccharides or polysaccharides processed into an amorphous floss by the simultaneous action of flash melting and centrifugal force. It is then partially recrystallized (or cured) to provide a compound with good flowability and compressibility for tabletting. Flashdose tablets of powder or coated miniparticles disperse rapidly, can accommodate high active doses, and possess satisfactory mechanical strength. The high temperature required to melt the matrix, however, can limit the use of the shearform matrix with heat-sensitive drugs.

Takeda (Osaka, Japan) has developed compression-moulded mixtures containing a drug and a combination of starches and sugars with surfaces that have been wetted with a suitable amount of water (11). The wetted mass is compression-moulded and dried, and porous tablets (with sufficient mechanical strength to resist destruction during further manufacturing) are obtained. The FMT, the weight of which can reach 1–2 g, has a sufficiently rapid disintegration time in the mouth (30–50 s according to examples reported in the patent application).

Novartis Consumer Health (Basel, Switzerland) also has filed a patent application for tablets prepared by dispensing the drug solution or suspension into moulds, evaporating the solvent from the units (usually achieved by heating, pressure reduction, or microwave radiation), and then optionally sealing the dried units directly in the mould (12). The patent application reported only examples of low-dose and low-weight forms, although higher amounts are claimed.

Nippon Shinyaku (Kyoto, Japan) compression-moulds and dries a kneaded mixture containing the drug and a water-soluble sugar (13). This process is claimed to impart sufficient physicochemical stability to the tablet, good appearance, and an oral cavity dissolution time of less than 30 s.

Direct compression. Direct compression is the easiest way to manufacture tablets and, therefore, FMTs. The great advantage of direct compression is the low manufacturing cost. It uses conventional equipment, commonly available excipients, and a limited number of process steps. Moreover, high doses can be accommodated in FMTs, the final weight of which can easily exceed that of other production methods.

The direct-compression tablet's disintegration and solubilization are based on the single or combined action of disintegrants, water-soluble excipients, and effervescent agents. The disintegration time is, in general, satisfactory, although the disintegrating efficacy is strongly affected (and limited) by tablet size and hardness. Large, hard tablets can have a disintegration time greater than that usually required for FMTs. As a consequence, products with optimal disintegration properties often have a medium–small size (weight) and/or a low physical resistance (high friability and low hardness). Breakage of tablet edges during handling, the presence of deleterious powder in the blistering phase, and tablet rupture during the opening of the blister alveolus all result from insufficient physical resistance.

In many cases, the disintegrants have a major role in the disintegration and dissolution process of FMTs made by direct compression. The choice of a suitable type and an optimal amount of disintegrants is paramount for ensuring a high disintegration rate.The addition of other formulation components such as water-soluble excipients or effervescent agents can further enhance dissolution or disintegration properties.

The understanding of disintegrant properties and their effect on formulation has significantly advanced during the last few years, particularly regarding so-called super-disintegrants (14). Caramella et al. found that disintegration efficiency is based on the force-equivalent concept (the combined measurement of swelling force development and amount of water absorption) (15,16). Force equivalence expresses the capability of a disintegrant to transform absorbed water into swelling (or disintegrating) force. The optimization of tablet disintegration was defined by means of the disintegrant critical concentration. Below this concentration, the tablet disintegration time is inversely proportional to the disintegrant concentration. Above the critical concentration, the disintegration time remains approximately constant or even increases (17). Different formulation routes were followed to achieve an optimal disintegration time in FMTs made by direct compression.

Ethypharm (Paris, France) recently launched Flashtab for multiparticulate actives (coated crystals and uncoated or coated microgranules) (18). The simultaneous presence of a disintegrant with a high swelling (or disintegrating) force, defined as "disintegrating agent," and a substance with low swelling force (starch, cellulose, and direct-compression sugar), defined as "swelling agent," was claimed as the key factor for the rapid disintegration of a tablet, also offering satisfactory physical resistance (19).

The Wowtab manufactured by Yamanouchi (Tokyo, Japan) is an intrabuccally dissolved compressed moulding comprising granules made with saccharides having low and high mouldability, respectively (20). In this context, the term *mouldability* is defined as the capacity of the compound to be compressed (moulded) and to dissolve rather than the formation of a true moulding by solvent wetting or melting. For example, low moulding means that the saccharide shows reduced compressibility by tabletting and, in general, a rapid dissolution. By contrast, a high-moulding saccharide shows excellent compressibility and slow dissolution. The Wowtab reportedly can accommodate high doses of multiparticulate water-soluble or insoluble drugs, dissolves rapidly, and has an adequate hardness (20,21).

Daiichi (Tokyo, Japan) performed a series of experiments to develop an FMT of moderate strength, using a combination of starch or cellulose and one or more water-soluble saccharides (22). Erythritol was found to be the best sugar for this type of formulation, showing rapid disintegration that was negligibly affected by tablet hardness; good tolerability and sweetening; and a refreshing mouth sensation because of its endothermic dissolution heat.

The Orasolv technology from Cima Labs (Eden Prairie, MN) is an example of a slightly effervescent tablet that rapidly dissolves in the mouth (23). The product is a slightly effervescent FMT containing multiparticulate forms, which also can accommodate high doses. The disintegra-

Table II: Characteristics of different Ziplets formulations.

	Formulation A	Formulation B	Formulation C
Dose (mg)	450	200	20
Weight (mg)	850	513	228
Diameter (mm)	16	13	9
Hardness (N)	49	31	18
Friability (%)	1.1	0.7	0.7
In vivo disintegration(s)	40	25	15

tion of FMTs in the mouth is caused by the action of an effervescent agent, activated by saliva. It also is said to provide a distinct, pleasant sensation of effervescence (fizzing or bubbling) in the mouth of the patient. The microcapsules are loosely compressed to maintain the integrity of the particle coating. However, as a consequence of this process, the physical resistance of the tablets is negatively affected.

Other examples of effervescent application include a glycine-based low-dosage aspirin tablet produced by Top Laboratories (Greenwich, CT) (24) and a product from Lab Pharm Res (Laval, Quebec, Canada) comprising one or more effervescent and disintegrating compounds for a synergic action of disintegration and dissolution (25). The main drawback of using effervescent excipients is their inability to prevent moisture absorption. Manufacturing requires a controlled environment at low relative humidity (RH) and protection of the final tablets with moisture-impermeable blisters. As a consequence, the cost of FMTs is higher than the cost of standard tablets made by direct compression, despite the lower cost profile compared with other, more sophisticated technologies.

Recent research also has begun into direct-compression FMTs. Mathematical regression studies have been done to determine the optimum combination of both physical characteristics (such as porosity and tensile strength) and formulation components in tablets made of cellulosic compounds and saccharides (26,27). Rapidly disintegrating tablets with durable structures and pleasant tastes were then prepared with the identified optimal parameters.

Technology developments

It is evident that the main challenge in developing an FMT is to achieve both good physical resistance and disintegration properties. Generally, a traditional direct-compression approach is preferred because it offers low production costs and the use of commonly available equipment and materials.

On this basis, Eurand (Pessano con Bornago, Italy) recently developed the Ziplets technology, which can be used with water-insoluble compounds as both bulk actives and as coated microparticles (the latter containing soluble and/or insoluble drugs) (28). It was found that the addition of a suitable amount of a water-insoluble inorganic excipient combined with one or more effective disintegrants imparted an excellent physical resistance to the FMT and simultaneously maintained optimal disintegration, even at low compression forces and tablet hardnesses (28). Examples of formulations at different doses and tablet weights are reported in Table II, and demonstrate that satisfactory properties (such as hardness, friability, and disintegration time) can be obtained at a high dose (450 mg) and weight (850 mg). In fact, handling problems during manufacturing (breakage of the tablet edges or formation of powder, which adversely affects the blistering phase) are avoided because of mechanical resistance. The risk of tablet breakage during the opening of the blister pack is eliminated.

The use of water-insoluble inorganic excipients also offers better enhancement of disintegration characteristics than most commonly used water-soluble sugars or salts. In fact, tablets composed primarily of water-soluble components often tend to dissolve rather than disintegrate, resulting in a much longer disintegration time. As the soluble components dissolve on the tablet's outer layer, the rate of the water diffusion into the tablet core decreases because of the formation of concentrated viscous solutions (14).

The stability of the Ziplets tablets is shown in Table III. Only negligible changes in their physical properties and disintegration time were observed after six months at accelerated conditions (40 °C, 75% RH) and after 18 months at 25 °C, 60% RH. The results of Tables II and III demonstrate the suitability of this technology for producing an optimal FMT of water-insoluble compounds at a cost equal to that of standard fast-release tablets.

Disintegration test

The definition of fast-melting (or disintegrating) tablet appeared in a compendial publication for the first time in 1998. So far, neither the US Pharmacopeia nor the European Pharmacopoeia have defined a specific disintegration test for FMTs. Currently, it is only possible to refer to the tests on dispersible or effervescent tablets for the evaluation of the disintegrating capacity of FMTs (29).

In our experience, the results obtained using the compendial test for dispersible tablets only approximate the actual disintegration time in the mouth. In some cases, a much higher or lower in vitro disintegration time than that of the in vivo test also was found. The compendial disintegration test showed good correlation with the in vivo data only within the same family of formulations or during the stability testing of a single formulation. The term *family* indicates formulations having the same qualitative composition and quantitative ingredient variations sufficiently limited to not markedly affect the general characteristics of the tablets.

Although the compendial test for dispersible tablets can be applied to FMTs with certain limitations, it is still necessary to define a suitable method to better discriminate between the disintegration times of FMTs and to better correlate in vitro and in vivo data. To achieve this goal, a modified dissolution apparatus was applied to an FMT with a disintegration time that was too fast to distinguish the differences between the tablets when the compendial method was used (27). A basket sinker containing the tablets was placed just below the water surface in a container with 900 mL of water at 37 °C, and a paddle rotating at 100 rpm was used. The disintegration time was determined when the tablet completely disintegrated and passed through the screen of the sinker.

In another case, a texture analysis apparatus was used to measure the start and end time points of tablet disintegration (21). A constant penetration force was applied to tablets via a cylindrical flat-ended probe. The tablet, under constant force, was immersed in a defined volume of distilled water, and the time was plotted against the distance the probe travelled into the tablet. Typical time–distance profiles, generated by the texture-analysis software, enabled the calculation of the starting and ending disintegration times. Both the new methods were able to satisfactorily discriminate between tablets of different formulations or properties and could perhaps be taken into consideration as a useful test.

Table III: Stability of two different Ziplets formulations (HDPE bottle as primary packaging).

		Formulation A	Formulation B
Dose (mg)		400	200
Weight (mg)		850	513
Diameter (mm)		16	13
Hardness (N)	Time zero	49	31
	6 months: 40 °C and 75% RH	42	52
	12 months: 25 °C and 60% RH	48	–
	18 months: 25 °C and 60% RH	–	49
Friability (%)	Time zero	1.1	0.4
	6 months: 40 °C and 75% RH	1.5	0.3
	12 months: 25 °C and 60% RH	0.9	–
	18 months: 25 °C and 60% RH	–	0.4
In vivo disintegration (s)	Time zero	40	30
	6 months: 40 °C and 75% RH	35	45
	12 months: 25 °C and 60% RH	40	–
	18 months: 25 °C and 60% RH	–	35

Clinical studies

In vivo studies were performed on oral fast-disintegrating dosage forms to investigate their behaviour in the oral–oesophageal tract, their pharmacokinetic and therapeutic efficacy, and acceptability. Zydis's residence time in the mouth and stomach, and its transit through the oesophageal tract, was investigated using gamma-scintigraphy. Its dissolution and buccal clearance was rapid (30); the oesophageal transit time and stomach-emptying time were comparable with those of traditional tablets, capsules, or liquid forms (31,32). A decreased intersubject variability in transit time also was observed (31). Zydis also showed good therapeutic efficacy and patient acceptability — particularly in children (33,34) or when easy administration and rapid onset of action were required (such as for patients undergoing surgery) (35,36).

The fast-disintegrating forms examined showed improved pharmacokinetic characteristics when compared with reference oral solid formulations. For example, the absorption rate of the acetaminophen Flashtab was higher than that of the brand leader, while having the same bioavailability (37). Increased bioavailability and improved patient compliance were observed in Lyoc formulations for different drugs such as phloroglucinol (6,38), glafenine (38), spironolactone (6), and propyphenazone (6,39). Using Zydis, all the drugs that can be absorbed through the buccal and oesophageal mucosa exhibited increased bioavailability and side-effect reduction. This is helpful particularly in actives with marked first-pass hepatic metabolism (4,30). Finally, the suitability of FMTs for long-term therapy also was assessed. Lyoc formulations containing aluminum were positively tested in patients with gastrointestinal symptoms (40).

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