Expert Opinion

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Frosta®: a new technology for making fast-melting tablets

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The fast-melting tablet (FMT) technology, which is known to be one of the most innovated methods in oral drug delivery systems, is a rapidly growing area of drug delivery. The initial success of the FMT formulation led to the development of various technologies. These technologies, however, still have some limitations. Recently, a new technology called Frosta® (Akina) was developed for making FMTs. The Frosta technology utilises the conventional wet granulation process and tablet press for cost-effective production of tablets. The Frosta tablets are mechanically strong with friability of < 1% and are stable in accelerated stability conditions when packaged into a bottle container. They are robust enough to be packaged in multi-tablet vials. Conventional rotary tablet presses can be used for the production of the tablets and no other special instruments are required. Thus, the cost of making FMTs is lower than that of other existing technologies. Depending on the size, Frosta tablets can melt in < 10 s after placing them in the oral cavity for easy swallowing. The Frosta technology is ideal for wide application of FMTs technology to various drug and nutritional formulations.

Keywords: fast-melting tablet, Frosta®, highly plastic granules, highly porous structure, plastic material, water-penetration enhancer, wet binder

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1. Introduction

Oral drug delivery has been considered to be the most convenient among all the routes of drug administration. Solid dosage forms, such as tablets and capsules, have been used most widely due to their advantages including accurate dosing, good stability, easy manufacturing, small packaging size and easy handling by patients. However, many patients have difficulty in swallowing solid dosage forms mainly due to their size. Appreciation of such limitations has led to the development of new oral dosage forms in order to improve patient compliance.

Fast-melting tablet (FMT) is a recent innovation in oral formulations and has become a fast-growing segment of the drug delivery technologies. FMT is also known as a fast-disintegrating, fast-dispersing, rapid dissolving, rapid melting and/or quick disintegrating tablet. The FDA named all the approved FMTs as 'orally disintegrating tablets'. Moreover, the European Pharmacopeia used the name 'orodispersible tablet' for these kind of dosage forms. The fast-melting dosage forms, which can be administered easily without any water, are suitable for all age groups but especially for children, the elderly and those who have some difficulty in swallowing conventional solid dosage [1].

The initial success of the first FMT formulation led to the development of different technologies. The FMT technologies can be classified as the following: freeze drying, molding/sublimation or compression. Whatever technology is used, the important properties of successful FMTs are instant absorption of water into the core of the tablets and then the fast disintegration of associated particles into separate components [2].

This fast-melting technology has advantages of solid dosage forms, such as easy handling and low cost of production, as well as advantages of liquid formulations, such as easy administration and no suffocation risk resulting from physical obstruction by a solid dosage form [3-5]. In fact, the application of FMTs can be extended to more general patients requiring daily medication. Moreover, from the point of view of the pharmaceutical industry, FMTs can provide a new dosage form strategy as a life cycle management tool for drugs that are near the end of their patent protection period.

Although there are many advantages, the FMT technology also has some limitations. Following introduction on the tongue these tablets dissolve or disintegrate quickly in the absence of water for the easy administration of drugs. However, it is challenging to keep the tablet strong while maintaining fast-melting properties. A balance between fast disintegration and high mechanical strength of the tablet is critical to the development of successful formulations. Moreover, fast disintegration in the mouth may limit the number of drugs that can be loaded into the FMT formulations. For example, many drugs are unpalatable and unpleasant in taste. After the tablet disintegrates or dissolves in the saliva, the drug in the tablet remains in the oral cavity for a while until it is swallowed. If the drug has an unfavourable taste, it will cause problems regarding patient compliance. High drug loading is another challenge for the formulation development. It is dependent on the physicochemical properties of the drug and the formulation properties. If the drug is unstable at low pH, it is very important to apply a method to circumvent the gastric environment so that the drug will not be degraded chemically and to prevent any issue of bioavailability.

Successful FMTs should be mechanically strong, fast in disintegration, have a pleasant in-mouth feeling, leaving no or minimum residue in the mouth, possible for high drug loading, and portable without any friability problems. They should be insensitive to temperature and humidity. Despite many hurdles to overcome, the FMT formulations have been gaining ever increasing acceptance by patients.

2. Major fast-melting tablet technologies

There are several commercially available FMT technologies, which can be classified as freeze drying, molding or compression based on the method of tablet preparation. They have already been well reviewed in the literature [1,2,4,6]. Among the technologies, the freeze drying and compression method are most widely used (**Table 1**). Each technology has its advantages and limitations, but no single technology has all the desirable properties of the ideal FMT.

2.1 Freeze-drying method

Freeze drying is a process in which solvent is removed from the frozen matrix of a drug solution or a suspension containing structure-forming excipients. The resulting dried tablets are very light and have highly porous structures. When placed on the tongue, the tablet dissolves almost instantly to release the incorporated drug. The entire freeze-drying process takes place at non-elevated temperatures to ensure there is no adverse thermal effect, which may affect the drug stability during the process. The freeze-drying process may result in an amorphous structure of excipients as well as drug substances, leading to the enhanced dissolution rate [5,6].

Table 1. Examples of commercialised FMT technologies using freeze-drying and compression methods.

Technology base	Technology	Company
Freeze drying	Zydis®	Cardinal Health
	Lyoc®	Cephalon
Compression	OraSolv/DuraSolv®	Cima Labs
	WOWTAB®	Yamanouchi Pharma
	Flashtab®	Ethypharm
	AdvaTab®	Eurand
	OraQuick®	KV Pharmaceutical
	Pharmburst™	SPI Pharma

FMT: Fast-melting tablet.

The most well-known example of the freeze-drying method is the Zydis® (Cardinal Health) technology. This is the first marketed formulation, and there are > 12 products based on this technology on the market. Examples include Claritin® Reditab® (Schering Plough), Dimetapp® Quick Dissolve (Wyeth), Pepcid® RPD (Merck), Zofran® ODT® (Glaxo-SmithKline), and Zyprexa® Zydis® (Eli Lilly and Co). However, the freeze-dried tablets are too fragile to withstand the pressure of being pushed through the foil of a conventional blister package, and thus, special packaging has been used. There are some requirements for applying the Zydis technology. The particle size of a drug should be < 50 µm because precipitation may occur during manufacturing if large drug particles are used [5]. In addition, drugs should be chemically stable and water insoluble because water-soluble drugs may form eutectic mixtures that cannot be frozen properly to make a rigid structure after the removal of solvents [5]. If the structure cannot support itself, it may cause the freeze dried cake to collapse; therefore, the maximum dose of water-soluble drugs is usually limited to ~ 60 mg [5]. The freeze-dried dosage form may degrade at humidity of > 65%, therefore any damage to the package may cause collapse of the tablet [7]. Special care is necessary for this dosage form and packaging.

2.2 Compression method

The use of the conventional rotary tablet press in the compression method for making FMTs is very attractive because of the high mechanical strength of the tablets, low manufacturing cost, consistent and robust process, and easy technology transfer. In fact, there are several commercially available technologies. Cima Labs developed Orasolv® technology,

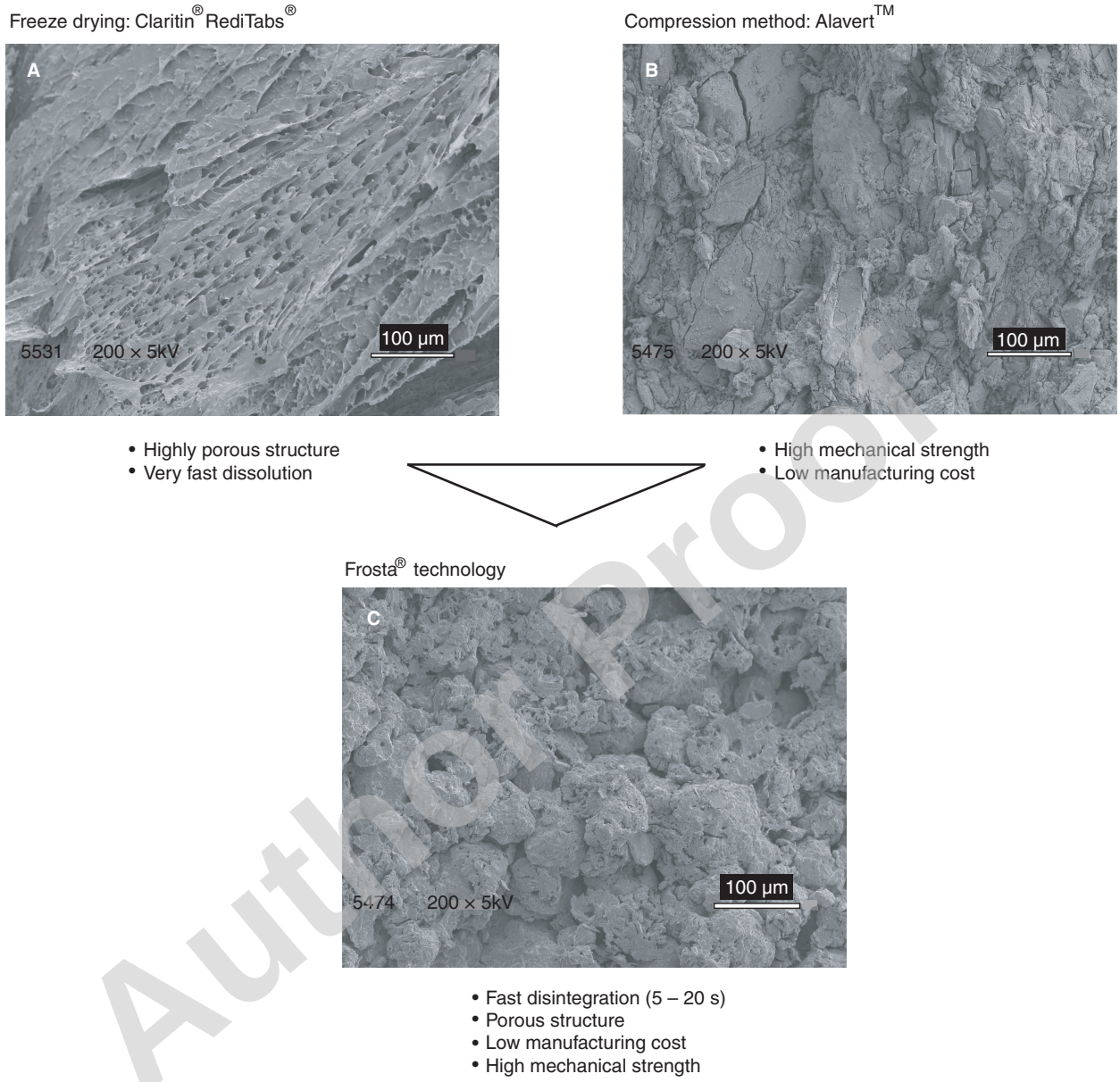

Figure 1. Scanning electron microscope pictures of horizontal cross sections of tablets from A. Claritin® RediTabs®, B. Alavert™ Loratadine ODT, and C. Frosta® tablet (magnification 200×) and their major advantages.

which uses a low compression pressure to make tablets for the manufacturing process [101,102]. It utilises effervescent excipients in its formulation, which can release gas following contact with water. The effervescent excipients usually contain pairs of an acid and a carbonate source. The acid source can be citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, or succinic acids. The carbonate source can be sodium bicarbonate, sodium carbonate, potassium bicarbonate, or potassium carbonate. The resulting carbon dioxide from the reaction may decrease the disintegration time and provide patients with some positive sensation.

Durasolv® technology was developed later by the same company to provide a tablet with enough mechanical strength to be packaged in blisters or bottles [103]. The important ingredients of the technology are nondirect compression fillers, which have the advantage of fast dissolution and prevent the gritty feeling that is usually present in direct compressible version of the fillers. The particle size of the nondirect compression fillers is 20 – 65 µm. However, ≥ 80% of the particles are > 100 µm in size for direct compressible fillers. Examples include dextrose, mannitol, sorbitol, lactose and sucrose. The tablets have low friability (≤ 2%) when tested according to the

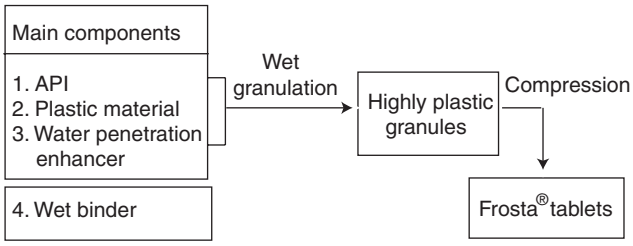

Figure 2. A simplified manufacturing process of highly plastic granules and their fast-melting tablets.
API: Active pharmaceutical ingredient.

United States Pharmacopeia (USP), and the hardness of the tablets is ~ 15 – 20 N with a fast disintegration time of < 60 s.

WOWTAB® technology (Yamanouchi Pharma) is based on the manufacture of granules using saccharides with high and low moldabilities. The tablets obtained by the compression method have to undergo special moisture treatment to increase the tablet strength [104,105]. Flashtab® technology (Ethypharm) produces tablets by the compression of granular excipients [106]. AdvaTab™ technology (Eurand) utilises an external lubrication system, in which lubricants are sprayed onto each tablet during the production process [107]. This technology can use a smaller amount of hydrophobic lubricants so the tablets do not block the absorption of water into the tablet matrix following contact with water, resulting in fast disintegration. However, this external lubrication system is not as efficient as an internal system, in which a lubricant is dispersed throughout the granules before tableting.

Slow dissolution or disintegration of compressed tablets containing highly water-soluble excipients is likely to be due to the low porosity of the tablets, which can reduce water penetration into the tablet matrix. Many strategies have been tried using a tablet press to achieve higher porosity with adequate tablet strength. For example, when volatile materials such as urea, ammonium carbonate and camphor are compressed with other excipients into the tablets, porous structures can be achieved after they are sublimated [108]. Another approach is to compress tablets at a low pressure and apply 'after treatments', such as moisture treatment, to the tablets in order to obtain enough tablet strength. However, these technologies still have some limitations, and none of them have all the desirable properties of the tablets. Consequently, it was necessary to develop a new technology that met all the required properties, including fast melting with sufficient mechanical strength and good friability, low manufacturing cost, robust process and easy handling.

3. Frosta® fast-melting tablet technology

Even though the Frosta® (Akina) technology is not the first FMT technology developed based on the compression method, it is unique because it combines two contradicting properties into one formulation: fast disintegration and high mechanical strength. The Frosta technology is based on the compression of highly plastic granules at low pressures to prepare FMTs [8]. The highly plastic granules are composed of three components: a plastic material, a water-penetration enhancer and a wet binder. Each of the three components play an essential role in obtaining tablets with higher strength and faster disintegration time than the other FMTs. The key benefits of the Frosta technology are:

- fast disintegration in the mouth: within 5 – 40 s depending on the tablet size
- low manufacturing cost: the same as making conventional tablets
- simple processing: one-step wet granulation processing
- strong mechanical property: friability < 1%
- multi-tablet packaging: dozens of tablets in one bottle

Several commercially available FMTs were investigated using scanning electron microscopy in order to understand the important properties necessary for making good FMTs. As shown in **Figure 1A**, the inner structure of a freeze-dried tablet (Claritin RediTabs) shows that a lot of pores are connected to each other and the pore sizes are > 10 µm. The presence of many pores allows the saliva to penetrate into the tablet easily and disrupt the tablet structure very quickly. However, the tablet is so weak that a special packaging is necessary to prevent the breakage of the tablet during shipping or handling. On the other hand, the compressed tablet (Alavert™, Wyeth Consumer Healthcare) in **Figure 1B** shows lack of pores, which may explain the longer disintegration time of the compressed tablets than that of the freeze dried. However, the mechanical strength of the compressed tablets is much higher than that of the freeze dried. The Frosta technology takes advantages of both technologies by maintaining porous structures inside the compressed tablets as shown in **Figure 1C**.

For optimum tablet properties, three components were used to prepare highly plastic granules that could be compressed at low pressures and yet maintain the porous structure for fast absorption of water into the tablet core. **Figure 2** shows the processing step for making highly plastic granules and FMTs. The main components used are plastic material, a water-penetration enhancer and binder. It is critical to select suitable excipients for preparing highly plastic granules.

A wet granulation method is used to prepare highly plastic granules. For example, Maltrin® QD 580 (Grain Processing Corp.) of size between US Standard Testing Sieve No. 20 and No. 60 sieve and Mannogem EZ spray (spray-dried mannitol, SPI Pharma., Inc., New Castle, DE) particles were put into a high shear granulator (Diosna Dierks & Söhne GmbH) and mixed in dry state for 30 sec. Subsequently, sucrose solution was pumped into the mixer by a peristaltic pump (Minipuls 2) until all of the binder solution was introduced. The mixing continued for 2 min more, and the wet mass was passed through a No. 8 sieve. After

drying the granules, they were blended with lubricants in the Servolift Desktop Labortory Bin blender. The granules were compressed into tablets by a Carver press or a rotary tablet press (Betapress Model 13U18). **Figure 3** shows the Frosta tablet properties corresponding to the different compression pressure. As the pressure increased, tablet tensile strength increased linearly, but porosity decreased exponentially in the tested range. When compressed at 300 lbs, the porosity and wetting time of the resulting tablets were 30% and 2 s, respectively.

3.1 A plastic material

When the same material is used for making FMTs, the mechanical strength of tablets is increased when the porous granules are used. For example, Maltrin QD M580 and Maltrin M180 are maltodextrin and corn syrup solids with the same dextrose equivalent value, which is 18. The only difference is density. Maltrin QD 580 is porous with a packed density of 0.40 g/cc, whereas Maltrin M180 is nonporous material with the packed density of 0.61 g/cc. Maltrin M180 is specially treated so that the Maltrin M180 particles are agglomerated making low-density Maltrin QD M580 with a highly porous structure. When granules were prepared with 20 and 80% by weight of Maltrin QD 580 and Mannogem EZ Spray, and 20 and 80% by weight of Maltrin M180 and Mannogem EZ Spray, respectively, the hardness of the tablets with Maltrin QD 580 and Maltrin M180 was 65.2 N and 7.3 N, respectively [8]. Because of its porous structure, the Maltrin QD M580 granules created more plastic deformation than the Maltrin M180 granules

The high mechanical strength of tablets made of the porous Maltrin QD M580 granules is not quite surprising. It was shown that when microsponges, which are porous polymeric microspheres, and drug were mixed, the mixture showed higher compressibility due to the plastic deformation of the sponge-like structure of microsponges [9]. When mechanical properties of low-crystallinity powdered celluloses were evaluated, the materials started plastic deformation at relatively low compression pressures whereas the total volume reduction was comparable to microcrystalline celluloses and powdered celluloses [10]. Granules with large pores showed low compression energy losses. They are also more prone to particle rearrangement, plastic deformation and brittle fracture following compression leading to the increased tablet mechanical strength [11].

3.2 A water-penetration enhancer

The two major components of highly plastic granules are a plastic material and a water-penetration enhancer. In general, the proportion of the two components needs to be adjusted to obtain the optimal tablet properties. If a large portion of a water-penetration enhancer is dissolved during the granulation process, it would cause the granules to lose their plasticity resulting in the low mechanical strength of the tablets. For example, when various ratios of the Mannogem EZ Spray and

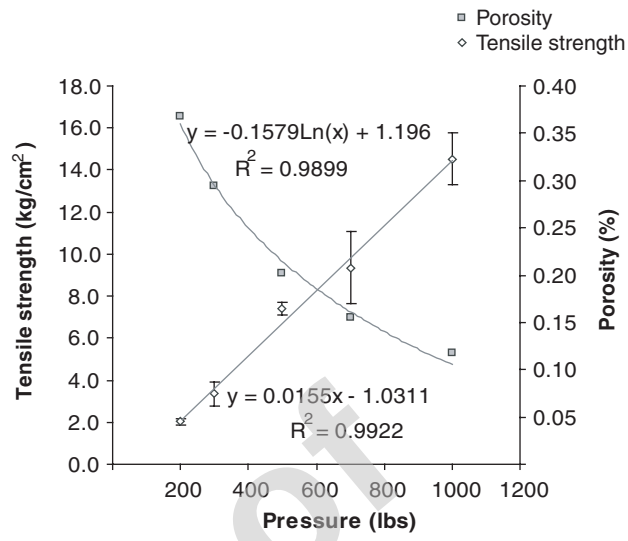

Figure 3. Changes in tablet tensile strength and porosity as a function of compression pressure.

Maltrin QD M580 were mixed and granulated using the same amount of a wet binder, the tablet hardness, as well as the tablet disintegration time, increased as the proportion of Mannogem EZ Spray was increased [8]. The optimal proportion of the two components needs to be identified for the desirable mechanical strength and the disintegration time.

3.3 A wet binder

Compressing the mixture of a plastic material and a water-penetration enhancer did not produce tablets with a desirable mechanical strength. It was necessary to add a binder during the wet granulation process to achieve a good bonding effect between the types of particles, thus resulting in high mechanical strength. Moreover, the type and concentration of the binder in solution had to be adjusted to make granules with desirable physical properties.

One of the most common binders is sucrose. When a mixture of a plastic material and a water-penetrating enhancer was granulated using different concentrations of sucrose ranging from 10 to 70%, the stronger tablets were obtained as the higher concentration of sucrose was used. This is most likely due to more plastic deformation of the granules and thus better bonding [8]. The most important benefit of using binder solutions with high concentrations is that the porous structure of a plastic material and a water-penetrating enhancer are preserved during the wet granulation step. The solidified binder of the dried granules dissolved instantaneously on contact with the saliva or water. There are many other polymeric binder solutions, such as polyvinylpyrrolidone and hydroxypropyl methylcellulose, which have been used to prepare tablets [12]. However, the high viscosity of the polymer solutions makes it difficult to apply. Furthermore, the presence of a polymer in the tablet

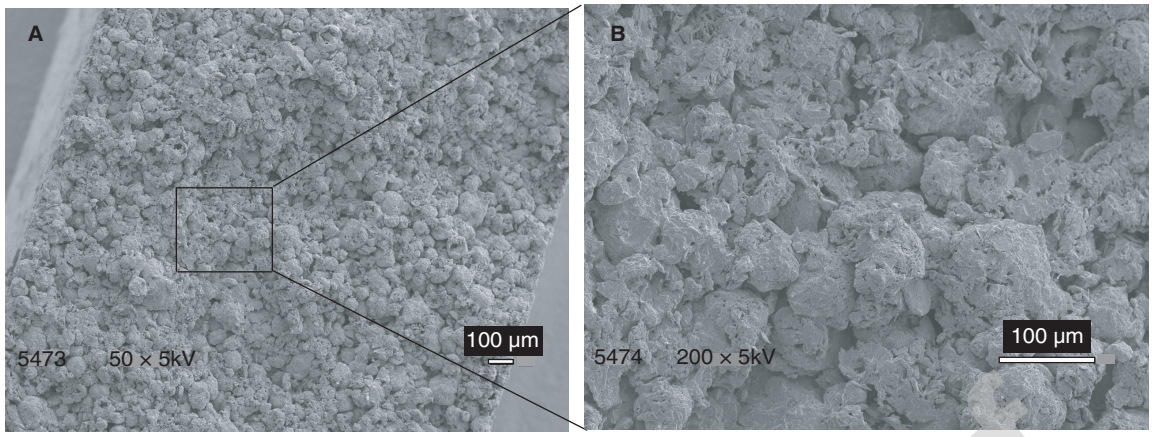

Figure 4. Scanning electron microscope pictures of a horizontal cross section of a Frosta® tablet based on the highly plastic granules in A. low (50×) and B. high magnifications (200×).

becomes a gel on contact with water or saliva, and the gel layer tends to retard further absorption of water into the tablet core.

3.4 Microscopic observation of a Frosta® tablet

As shown in **Figure 4**, the inner structure of a Frosta tablet shows the presence of many pores between the granules throughout the tablet matrix. It is these pores that increase the absorption of water by capillary force. On contact with saliva or water, the granules can be easily dissociated, and the whole tablet disintegrates to form a paste, which is very easy to swallow. **Figure 4A** shows the presence of highly plastic granules forming a tablet, and **Figure 4B** shows the presence of pores among the highly plastic granules, which is thought to be responsible for the fast absorption of water into the tablet core.

3.5 Important considerations of the 'three-component system'

A plastic material in the Frosta tablets can be water soluble or water dispersible, and can also be porous. Plastic deformation of the materials can improve the interparticle bonding necessary for better mechanical strength of the tablet. As mentioned above, if a plastic material is polymeric, it may build a viscous layer on the tablet surface on contact with water. The viscous layer may prevent water penetration into the tablet matrix causing slow disintegration. One way of preventing such a problem is to mix the plastic material with a water-penetration enhancer at a certain ratio and compress them at low pressure. This will give plastic deformation of the materials, creating intimate contact among the particles. In this process, the plastic particles can be separated from each other by water penetration-enhancing particles, which may prevent the formation of the viscous layer on the tablet surface.

Although the plastic materials can make close contacts to increase the chance of bonding by compression, formation of adequate bonding among the granules at a low compression pressure requires a suitable binder. The binder here can also prevent segregation of the porous materials and the water-penetration enhancers during mixing and granulation. If the binder is in a liquid or semisolid state, it should not significantly destroy the porous structure of the materials. One method of avoiding this is to apply higher concentrations of the binder to make the water activity lower. Another way is to allow only a short contact time with the porous structure when making granules using relatively low concentrations of the binder so that the porous structure would not be damaged by the binder solution.

3.6 Incorporation of drugs into the system

In the Frosta tablet processing method, active pharmaceutical or nutritional ingredients can be added at any stage during the process. They can be added to a mixture of plastic material and water-penetrating enhancer before making highly plastic granules, or alternatively, they can be blended with the highly plastic granules just before compression. Thus, the Frosta processing method provides high versatility in preparing FMTs, and thus is highly useful in the formulation of drugs with various properties. The simplicity of the processing method allows the incorporation of a drug in microparticles for the purpose of taste masking or sustained release.

4. *In vitro* testing of Frosta® fast-melting tablets

4.1 Disintegration of Frosta® tablets

Although an *in vivo* tablet disintegration (or melting) test offers the most meaningful data, it may not be useful as a routine test method due to its high cost and time, as well as the issue related to the subjectivity. There are several alternative disintegration methods to be applied for this test, such as the modified USP method [13,14], texture analyser method [15,16],

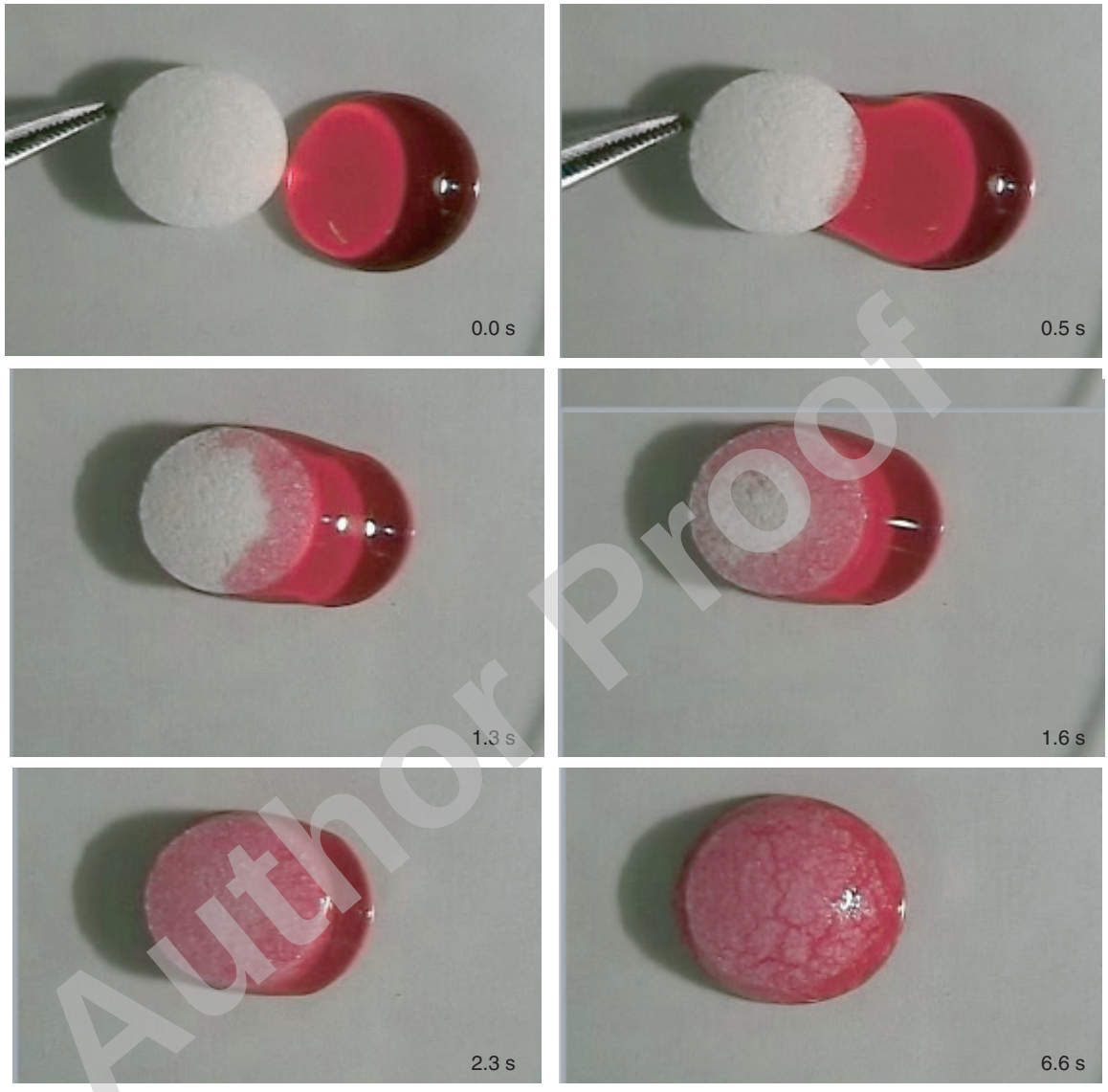

Figure 5. Photographs of water absorption and subsequent disintegration (or melting) process of a Frosta® tablet. The chronological order is given by the disintegration time in seconds.

couple-charge device camera method [17], rotary-shaft method [18] and sieve method [19].

For the Frosta tablets, the modified texture analyser method was mainly used [15,16] and the results were compared with the *in vivo* data. Texture Analyser (TA XT2®, Texture Technologies Corp.) was applied for this purpose. A tablet was adhered to the bottom of a probe, which was attached to a load cell, with a double-sided copper tape. In order to simulate a real condition, a wet filter paper with water or buffer, connected to a reservoir, was adopted as a disintegration medium. The attached tablet was compressed against the wet paper under a constant pressure. The probe distance would be steady as the tablet remained cohesive. However, once the tablet disintegrated, the compression distances increased because the probe had to keep the pressure constant. This increased rate continued until the tablet disintegrated. Using time-distance profiles, the disintegration time could be calculated.

Without any drugs in the Frosta tablet, the disintegration time was < 10 s, which it matched well with *in vivo* data. When a drug component was incorporated, the disintegration time was dependent on the physicochemical properties of the component. As shown in **Figure 5**, a blank Frosta tablet

Table 2. Basic properties and components of saliva [20].

Parameter	Value
Volume (ml/day)	500 – 1500
Rate of flow (ml/min)	0.6 (0.1 – 1.8)
Total protein (g/100 ml)	0.3 (0.15 – 0.64)
pH	6.7 (5.6 – 7.9)
Cholesterol (mg/100 ml)	7.5 (3 – 15)
Electrolytes (mM)	
Potassium	8 – 40
Sodium	5 – 100
Calcium	1.5 – 2
Phosphate	5.5 – 14
Chloride	5 – 70

absorbed water very quickly and melted instantly on contact with water forming a paste for easy swallowing.

4.2 Dissolution of fast-melting tablets

It may be desirable for the FMTs to be disintegrated (or melted) completely in the mouth, but there is no need for complete dissolution. Moreover, fast disintegration does not always mean fast dissolution. It is dependent on many properties of drugs, formulations and release media.

In vitro dissolution test methods of conventional tablets using simulated gastric and intestinal solutions are well established and documented in the pharmaceutical industry. The *in vitro* dissolution test is usually conducted according to USP 27 Apparatus 1 (basket method) or 2 (paddle method) guidelines with specific volume of dissolution medium maintained at 37 ± 0.5ºC. The composition of the media is 0.1N HCl for simulated gastric fluid and phosphate buffer for simulated intestinal fluid. However, *in vitro* dissolution test methods for the characterisation of FMTs are not well established. The current USP dissolution test was designed for conventional tablets, and no established test methods are currently available.

When the tablet is disintegrated on the tongue, the time for the disintegrated drug to travel from mouth to stomach is between 5 and 10 min [5]. Even though the time is short, it has been found that FMTs can promote pregastric absorption of the active ingredients through buccal, sublingual, oropharyngeal and oesophageal membranes, providing a rapid onset time of action and increased bioavailability. Pregastric absorption will reduce first-pass hepatic metabolism and side effect. Moreover, when a drug is partially dissolved in the oral cavity, patients can taste it. If the drug has a bad taste, patient compliance will be lost. Therefore, characterising dissolution in the oral cavity is very important. However, it may not be accomplished easily using current methodologies.

There are several differences in dissolution environments between the oral cavity and the gastrointestinal tract, such as volume, pH, composition of dissolution medium and tablet residence time. **Table 2** shows the composition and properties of the saliva [20]. It is important to simulate the *in vivo* dissolution environment (i.e., saliva) to obtain clinically useful data as the simulated gastric and intestinal fluids. As there is no recommendation for the dissolution medium in USP, the composition of the saliva may be modified based on the information presented in **Table 2** depending on the applications. In fact, dissolution in the oral cavity can be a valuable indicator or evaluation tool for taste-masking efficacy of the tablets [109].

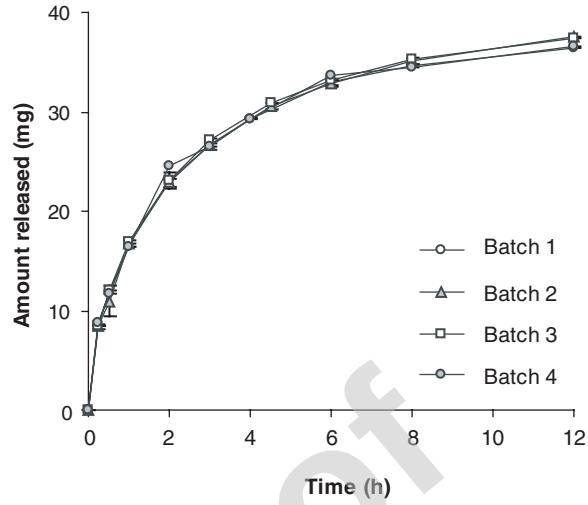

Figure 6. *In vitro* release of dextromethorphan from the controlled-release Frosta® tablets in two different batches. Drug-release profiles are the averages of at least three tablets in each batch.

5. Conclusion

FMTs can be easily administrated to patients. The popularity and usefulness of the initial formulation resulted in the development of several fast-melting technologies. The recently developed Frosta technology combines the major advantages of fast disintegration of freeze-dried formulations and high mechanical strength of compressed tablets.

Highly plastic granules were designed to be compressed at a low pressure for preparing the tablets with fast disintegration, higher mechanical strength and low friability. The highly plastic granules were composed of a plastic material, a water-penetration enhancer and a wet binder. All three components play an important role in obtaining tablets with optimum properties. The key properties of the Frosta tablet are its highly porous structure offering fast disintegration in the mouth and yet enough mechanical strength due to the highly plastic granules. The Frosta tablets are expected to improve patient compliance, provide a rapid onset time of action and increase bioavailability.

6. Expert opinion

One of the challenges for the development of fast-melting dosage forms is to mask the bad taste of some drugs. Many drugs are found to be unfavourable in their taste, especially when administered in liquid dosage forms, such as solution, emulsion and suspension. FMTs can be regarded as *in situ* suspension due to the fast disintegration [21]. After a tablet disintegrates in the oral cavity, drug molecules, which are dissolved or dispersed, in the tablet can stay in the mouth for some time until they are swallowed. In order to eliminate or reduce the negative feeling due to the poor taste of some drugs, various approaches have been tried to prevent drugs from interacting with taste buds. Many oral suspensions, syrups and chewable tablets simply contain flavours, sugars and other sweeteners to overcome or complement the bitter taste of the drug, and these methods can be applied to the fast-melting dosage forms. If those methods are not sufficient for masking bitter tastes then an additional method for taste masking is required, such as microencapsulation or complex formation.

Another challenge for the fast-melting dosage forms is to develop controlled-drug release formulations. As the Frosta processing allows the incorporation of drug-containing microparticles during the preparation of highly plastic granules, controlled-release property can be easily achieved for the Frosta FMTs. **Figure 6** shows an example of the sustained release of dextromethorphan (DM) for 12 h from the Frosta DM FMTs prepared by the rotary tablet press with the batch size of 100 g. Drug-release profiles were almost the same between the four batches, showing good reproducibility of the Frosta FMTs.

One of the most important challenges in the FMT formulations is to develop methods for loading drugs with very large doses. In general, fast-melting properties requires the presence of large amounts of excipients, and thus FMT formulations for large dose drugs will become very large. If the large dose drug is also bitter in taste, it really brings big challenges. It is, however, only a matter of time to find answers to such challenges.

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