# Discover new ways to improve ODT performance with Fuji F-MELT® system

## Introduction

An Oral Ddisintegrating Tablet (ODT) is defined as a solid dosage form that contains medicinal substances and disintegrates rapidly without water when placed on the tongue. Drug is released, dissolved or dispersed in the saliva and swallowed and absorbed across the gastro intestinal tract. The US FDA ODT guideline suggests 30 seconds *(in vitro)* as the preferred disintegration time whereas the disintegration time recommended by European pharmacopoeia is less than 3 minutes[1,2]. In Europe, the ODTs are referred to as Orodispersible preparations and ODT development has been relatively slow when compared to United States of America. In Japan, guidelines for ODTs have not been formerly released yet, so it is essential to keep in mind how important a definition of ODT could impact ODT formulator's decisions.

ODTs are becoming increasingly popular due to its ease of administration among all patient groups. Although ODTs were developed initially to overcome problems related to swallowing traditional solid dosage forms by pediatric and geriatric patients, a recent survey suggested that ODTs are preferred over conventional tablets. Since its inception in the 1980's, ODTs are one of the fastest growing segments of the oral drug delivery industry today. Perhaps another reason for the rise of ODT, is the possibility of extending product lifecycle through patented ODT technology with existing API. Currently, several products have reached the market, based on different approaches and technologies to achieve ODT.

Lyophilization and direct compression of a ODT excipient system are the two mainstream technologies that are used to develop ODTs. For lyophilized dosage forms, disintegration is extremely rapid but there are limitations. It has been reported that the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. Furthermore, those tablets are fragile and require special packaging and storage. On the other hand, direct compression of ODT excipients tends to be attractive because the process allows conventional tabletting equipment and materials to be used. This could amount to lower production costs when compared to lyophilization. However, ODT excipients category also requires careful evaluation because several patented powder systems are currently available. Optimum hardness, disintegration time, and mouth feel represents a multi-faceted challenge for ODT formulators. This article takes a closer look at Fuji's patented F-MELT® system which was specifically designed for ODTs. Examples include Acetaminophen, Aspirin, Vitamin C and how F-MELT® can be fine tuned to achieve the desired performance.

## F-MELT® ODT System

F-MELT® is a co-spray dried powder in which inorganic excipients and disintegrant/s are homogenously dispersed in a carbohydrate complex. F-MELT® is available as Type C and Type M. Generally, Type C is suitable for pharmaceutical and nutraceutical formulations while Type M is for pharmaceutical preparations only. However, compatibility of API's and the regulatory status of the composition in each country may ultimately govern which type of F-MELT® can be used for. The ingredients that constitute F-MELT® Type C and Type M vary slightly as shown in Table 1.

Table 1. Ingredients of F-MELT® Type C and Type M

| F-MELT® Type C | F-MELT® Type M |
|---|---|
| D-Mannitol | D-Mannitol |
| Xylitol | Xylitol |
| Microcrystalline Cellulose | Microcrystalline Cellulose |
| Crospovidone | Crospovidone |
| Dibasic Calcium Phosphate Anhydrous (Fujicalin®) | Magnesium Aluminometasilicate (Neusilin®) |

Due to its unique composition, F-MELT® placebo tablets have a hardness greater than 100 N at a compression force less than 8 kN (Fig 1). The hardness can be compared to that of conventional tablets. However, a 30-40% load of acetaminophen or aspirin can bring down the tablet hardness to a region between 30 and 35 N at compression forces between 5.4 and 5.7 kN. Simply increasing compression force to compensate tablet hardness results in oral disintegrating time exceeding 30 seconds (Table 2). Knowing this could happen, two strategies are revealed to overcome this formulation challenge while maintaining high quality ODTs, by incorporating an additional excipient or by switching to a different lubricant (Fig 2). Successful improvements to the ODTs were determined under the following criteria: ~50 N tablet hardness, 30 second oral disintegration time; pleasant mouth feel and less than 1% friability (data not shown).

Fig 1. F-MELT® placebo tablets of both Type M and Type C

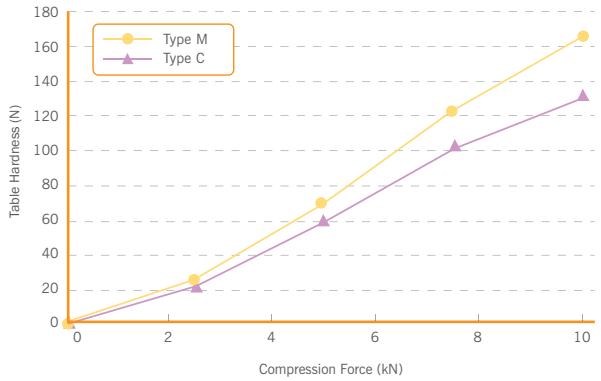
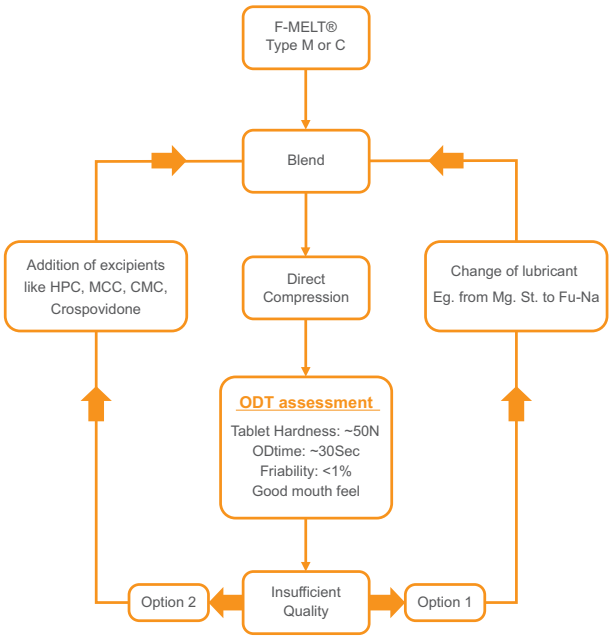



Table 2. ODT formulations with acetaminophen and F-MELT® Type M, Type C

| Acetaminophen (wt %) | 30 | 40 | 30 | 30 | 40 | 30 |
|---|---|---|---|---|---|---|
| Type M (wt %) | 69.6 | 59.6 | 69.6 | - | - | - |
| Type C (wt %) | - | - | - | 69.6 | 59.6 | 69.6 |
| Lubricant (Mg-St) (wt %) | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 |
| Compression Force (kN) | 5.4-5.7 | 5.9-6.4 | 7.5-8.0 | 5.5-5.8 | 8.1-8.7 | 9.0-9.5 |
| Tablet Hardness (N) | 36.4 | 30.2 | 59.8 | 31.7 | 36.6 | 49.1 |
| Oral Disintegration Time (sec) | 20.2 | 20.8 | 45.5 | 14.6 | 21.5 | 66.5 |
| Mouth Feel | Very Good | Very Good | Very Good | Very Good | Very Good | Very Good |

Mg-St-Magnesium Stearate, Tablets of 200 mg with 8 mm diameter were manufactured on a rotary tabletting machine.

Fig 2. Flow chart for preparing high quality F-MELT® tablets




HPC - Hydroxypropyl Cellulose, MCC - Microcrystalline Cellulose, CMC - Carboxymethyl Cellulose, Mg.St – Magnesium Stearate, Fu-Na - Sodium Stearyl Fumarate

## Optimizing F-MELT® ODT with additional excipients

The additional excipients added to the F-MELT® mix are microcrystalline cellulose (MCC), carboxymethyl cellulose (CMC), corn starch, hydroxypropyl starch (HPS), crospovidone and talc either alone or in combinations. For example, 30-50 % acetaminophen can be loaded with F-MELT® and 20% MCC or CMC or HPS to achieve a tablet hardness of 45-55 N with very good mouth feel and disintegration times less than 30 seconds (Table 3). However, excess addition of these ingredients can have a negative effect on the mouth feel sometimes resulting in gritty or sandy feeling. Table 4 summarizes the effect of ingredients on the mouth feel when added in excess, the rule of thumb is that they do not exceed 20%.

Table 3. Acetaminophen and Aspirin formulations with F-MELT® Type C.

| | Acetaminophen | | | Aspirin | | | |
|---|---|---|---|---|---|---|---|
| (wt %) | 30 | 30 | 40 | 40 | 40 | 40 | 40 |
| Type C (wt %) | 49.6 | 64.6 | 34.6 | 49.6 | 39.6 | 49.6 | 39.6 |
| Other Excipients (wt %) | 20 | 5 | 25 | 10 | 20 | 10 | 20 |
| | CMC | Crospovidone | MCC | CMC | MCC | Crospovidone | Corn Starch |
| Lubricant (Mg-St) (wt %) | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 |
| Compression Force (kN) | 12-13 | 11-12 | 6-7 | 7-8 | 4-5 | 6-7 | 9-10 |
| Tablet Hardness (N) | 44.7 | 50.4 | 58.2 | 43.6 | 48.6 | 41.6 | 49.2 |
| Oral Disintegration Time (sec) | 24.7 | 21.4 | 21.1 | 21.2 | 30.1 | 19.1 | 22.8 |
| Mouth Feel | Very Good | Very Good | Fair | Very Good | Good | Good | Good |

CMC- Carboxymethyl cellulose, MCC- Microcrystalline cellulose, Mg-St- Magnesium Stearate. Tablets of 200mg with 8mm diameter were manufactured on a rotary tabletting machine.

Table 4. Recommended dose of additional excipients to maintain better mouth feel

| Excipient | Negative effect on adding larger quantities | Recommended dosage |
|---|---|---|
| Corn starch | Mealy/ Fine powder | Less than 20% |
| Corn | Mealy | Less than 20% |
| MCC | Sandy/ Gritty | Less than 20% |
| CMC | Sour taste | Less than 20% |

## Optimizing F-MELT® ODT by selecting the right lubricant

Magnesium stearate is the common lubricant used in pharmaceutical industry for tablet manufacturing due to its safety records and ease of use. Sodium stearyl fumarte is a versatile disintegrant that shows superior performance over magnesium stearate with respect to tablet hardness variability and improved disintegration times. We found that by changing the lubricant to sodium stearyl fumarate, with or without additional excipients, one can prepare high quality F-MELT® ODT. Both acetaminophen(Table 5) and ascorbic acid showed similar trends with respect to tablet hardness and mouth feel (Table 6, 7).

Table 5. Acetaminophen formulations with F-MELT® Type M

| **Acetaminophen (wt %)** | **30** | **40** | **30** | **30** | **40** | **40** | **50** |
|---|---|---|---|---|---|---|---|
| Type M (wt %) | 69.1 | 59.1 | 69.0 | 69.0 | 59.0 | 59.0 | 49.0 |
| Talc (wt %) | 0.5 | 0.5 | - | - | - | - | - |
| Lubricant (Fu-Na) (wt %) | 0.4 | 0.4 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Compression Force (kN) | 6.0 | 9.0 | 4.7-5.0 | 6.7-7.0 | 5.7-6.5 | 8.4-9.2 | 7.0-8.0 |
| Tablet Hardness (N) | 53.4 | 55.6 | 39.2 | 63.1 | 44.7 | 63.8 | 35.3 |
| Oral Disintegration Time (sec) | 17.0 | 29.2 | 13.3 | 25.1 | 15.3 | 25.8 | 13.1 |
| Mouth Feel | Very Good | Very Good | Very Good | Very Good | Very Good | Very Good | Very Good |

Fu-Na: Sodium Stearyl Fumarate. Tablets of 200mg with 8mm diameter were manufactured on a rotary tabletting machine.

Table 6. Ascorbic acid formulations with F-MELT® Type C

| **Ascrobic Acid (wt %)** | **30** | **40** | **40** | **40** |
|---|---|---|---|---|
| Type C (wt %) | 69.0 | 58.5 | 59.1 | 59.1 |
| Talc (wt %) | - | 0.5 | 0.5 | 0.5 |
| Lubricant (Fu-Na) (wt %) | 1.0 | 1.0 | 0.4 | 0.4 |
| Compression Force (kN) | 4.8-5.2 | 8.0-8.6 | 5.1-5.4 | 7.0-7.4 |
| Tablet Hardness (N) | 30.8 | 49.5 | 32.1 | 45.8 |
| Oral Disintegration Time (sec) | 16.4 | 38.5 | 16.2 | 20.5 |
| Mouth Feel | Very Good | Very Good | Very Good | Very Good |

Fu-Na: Sodium Stearyl Fumarate. Tablets of 200mg with 8mm diameter were manufactured on a rotary tabletting machine.

Table 7. Ascorbic acid formulations with F-MELT® Type M

| **Ascrobic Acid (wt %)** | **30** | **30** | **40** | **40** |
|---|---|---|---|---|
| Type M (wt %) | 69.0 | 69.0 | 59.1 | 59.1 |
| Talc (wt %) | - | - | 0.5 | 0.5 |
| Lubricant (Fu-Na) (wt %) | 1.0 | 1.0 | 0.4 | 0.4 |
| Compression Force (kN) | 4.6-4.9 | 6.5-6.9 | 5.4-5.7 | 7.4-7.8 |
| Tablet Hardness (N) | 32.6 | 52.4 | 35.3 | 53.1 |
| Oral Disintegration Time (sec) | 17.4 | 27.7 | 13.8 | 24.3 |
| Mouth Feel | Very Good | Very Good | Very Good | Very Good |

Fu-Na: Sodium Stearyl Fumarate. Tablets of 200mg with 8mm diameter were manufactured on a rotary tabletting machine.

## Outlook:

With increasing number of ODTs coming to the market, the demand for developing ODTs with optimum hardness, faster disintegration times and good mouth feel rises accordingly. The trend will continue as patients accept ODTs as a dosage form with the convenience of having it anywhere, anytime and without water. Furthermore, ODTs may offer improved efficacy over conventional dosage forms or a chance to extend a product lifecycle for pharmaceutical companies. In this context, the F-MELT ® ODT system fills the gap where another technology may have limitations. F-MELT® is a royalty free user friendly, potentially cost saving, and flexible excipient system for nutraceutical and pharmaceutical industries. Lastly, the F-MELT® system can still meet the disintegration performance under the US FDA guideline even with 50 % API loads by either selecting the right lubricant or adding another excipient.

## Reference:


1. FDA, Guidance for Industry, Oral Disintegrating tablets Draft Guidance (Rockville, MD, April 2007)
2. European Pharmacopoeia 6.0; July 2007, Orodispersible Tablets


## Patent Information:

Composition for rapid disintegrating tablet in oral cavity, Patented in Japan, patent pending in USA, EU and India.