

Formulating Taste Masked and High Quality ODT of Poorly Water Soluble Drugs with F-MELT[®]

In this paper, we present case studies with taste masking technology and application of wet granulation technologies to develop ODTs of Loratadine, a water insoluble drug, and Famotidine, a slightly water soluble drug with bitter taste. Wet granulation approach was chosen to prepare ODTs of Loratadine and Famotidine and the tablets showed a very fast disintegration time as well as high dissolution rates. Bitterness of Famotidine could be eliminated by simple blending with flavors and sweeteners such as sucralose, acesulfame potassium, and micronized menthol.

INTRODUCTION

First appeared on market in 1980s, oral disintegrating tablets (ODTs) continue to grow in the pharmaceutical industry. Market research estimates the demand will reach 2.56 billion USD in 2012 and up to 3.9 billion USD by 2017⁽¹⁾. More and more pharmaceutical and nutraceutical companies are opting ODTs to differentiate generics as well as extend product lines. Generally accepted tablet qualities of ODTs include a tablet weight of less than 500 mg, a tablet hardness of approximately 50 N and a disintegration time of 30 seconds. US FDA guidance specifies that ODTs disintegrate rapidly in the oral cavity within a matter of seconds when placed on the tongue, or approximately 30 seconds or less *in vitro*⁽²⁾. Today, several platforms are available to the manufacturer of ODTs and the preference is tilting towards directly compressible excipient systems. However, for poorly water soluble drugs, wet granulation may still be the right choice for the manufacture of ODTs.



F-MELT[®], is a co-spray dried ODTs excipient system developed by Fuji Chemical Industry Co., Ltd. It includes 5 pharmaceutical excipients such as inorganic excipients, carbohydrates and disintegrants. Currently more than 10 pharmaceutical and nutraceutical customers in US, Japan, India and Korea have launched ODTs with F-MELT[®] and approximately 40 customers around the world are developing their ODTs formulations with F-MELT[®]. The common therapeutic targets of ODTs include allergies, nausea, migraine, schizophrenia, Alzheimer, gastric ulcer, diabetes, hypertension, anticoagulant, anti-cholesterol, antihistamines, sedatives, anti-emetics, cough/cold preparations, anesthetics, breath-fresheners/oral anti-septics, and pet drugs. Most of these drugs are bitter, which needs taste masking.

F-MELT[®] FAMILY

Fuji offers a choice of three different F-MELT[®] grades to formulators worldwide. F-MELT[®] family includes type C, suitable for pharmaceutical and nutraceutical applications, type M suitable for pharmaceutical applications, and F-MELT[®] F1 for dietary supplement as well as functional food applications (Table 1). With F-MELT[®], formulators can make high quality ODTs with high tablet hardness, good mouth feel and achieve disintegration time of less than 30



seconds. In certain cases, high API load formulations (40-50%) may reduce tablet performance such as reduction of tablet hardness and increase of disintegration time. For example, increasing compression force to compensate tablet hardness could increase disintegration time. With F-MELT[®], formulators can improve tablet qualities by simply switching to different lubricants and/or incorporating an additional excipient. In addition, preparing tertiary particles of APIs with F-MELT[®] by wet granulation using water or solvent could be a proper strategy to improve the quality and performance of ODTs (Fig. 1).

Table 1. Ingredients of F-MELT[®] Family

F-MELT [®] Type C Pharmaceutical and Nutraceutical applications	F-MELT [®] Type M Pharmaceutical applications	F-MELT [®] F1 Nutraceutical and Dietary supplement applications
D-Mannitol	D-Mannitol	Waxy rice starch
Xylitol	Xylitol	-
Microcrystalline cellulose	Microcrystalline cellulose	Microcrystalline cellulose
Crospovidone	Crospovidone	-
Dibasic Calcium Phosphate Anhydrous (Fujicalin [®])	Magnesium Aluminometasilicate (Neusilin [®])	Dibasic Calcium Phosphate Anhydrous (Fujicalin [®])

Figure 1. Flow Chart for Preparing High Quality ODTs with F-MELT[®] Family

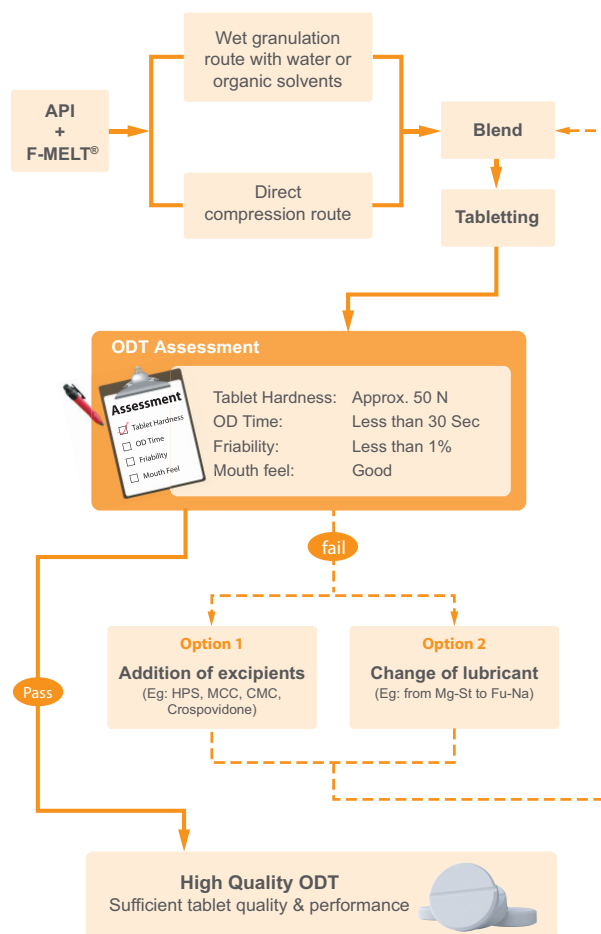


Table 2. The F-MELT[®] Features

- ✓ Ready to use excipient for ODTs
- ✓ Oral disintegration time less than 30 seconds
- ✓ Spherical shape with high flowability
- ✓ Directly compressible
- ✓ API loading more than 50% possible
- ✓ Tablet hardness more than 50 N possible with little or no sticking/capping
- ✓ Pleasant mouth feel
- ✓ No royalty or license fees required
- ✓ No special equipment required for tableting
- ✓ Easy handling and storage of ODTs with low friability

LORATADINE ODTs FORMULATION WITH F-MELT[®] TYPE M A SUCCESSFUL EXAMPLE WITH SOLVENT GRANULATION



Loratadine is a water insoluble drug belonging to antihistamine category, a target for ODTs market. Loratadine crystal particle size is less than 10 μm while F-MELT[®] mean particle size (D50) is 120 μm . Dry blending of F-MELT[®] or other excipients with

such low particle size APIs always pose big challenge to formulators. Wet granulation of Loratadine was attempted with both water and organic solvent. Water and/or solvent (water:ethanol=7:3) granulation of Loratadine was carried out with a portion of F-MELT[®] Type M (ratio 1:5). The granules were passed through No.25 sieve (710 μm) and dried overnight at 55°C. The dried granules were further passed through a No.60 sieve (250 μm) and blended with additional F-MELT[®] Type M and lubricant to prepare ODTs. The ODTs showed sufficient hardness (approx. 50N) and a disintegration time of less than 30s (Table 3). Dissolution was 99% with water granulation and 100% with solvent granulation (Fig 2). Granulating with 30% ethanol increased content uniformity (100%) when compared to water granulation (97%) of Loratadine with F-MELT[®] Type M. Dry blending and direct compression of Loratadine with same amount of F-MELT[®] type M resulted in poor content uniformity and dissolution (data not shown).

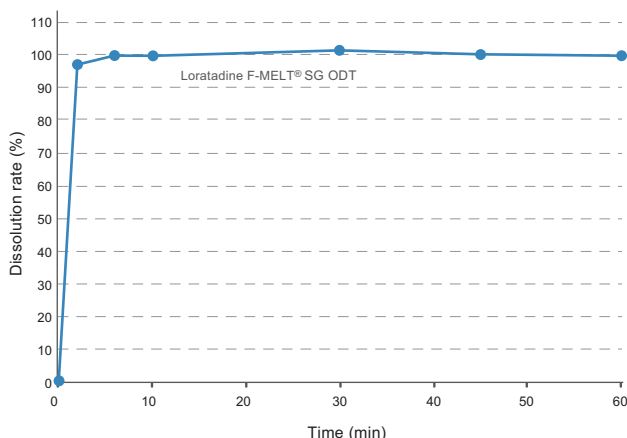
Table 3. Loratadine ODTs Formulations with F-MELT® Type M

Formulation	#1	#2
Water-granulated Loratadine with F-MELT® Type M (1:5)	60 mg	-
Solvent-granulated Loratadine with F-MELT® Type M (1:5)	-	60 mg
F-MELT® Type M	139.2 mg	139.2 mg
Magnesium Stearate	0.8 mg	0.8 mg
Total	200 mg	200 mg

Tablet Characteristics	#1	#2
Tablet hardness (N)	49.7	47.6
Pharmacopoeia disintegration time (s)	12.54	11.13
Oral disintegration time ODT-101*(s)	19.64	13.38

Tablet condition: Φ 8 mm, 200 mg/Tab, Rotary tableting machine

*Equipment to measure ODTs (Toyama Sangyo Co., Ltd.)

Figure 2. Dissolution Profile of solvent granulated (SG) Loratadine ODTs Formulation

Dissolution was carried out with JP disintegration test solution #1 (pH 1.2), 900 ml, 37°C, paddle speed 50 rpm.

Stability tests of solvent granulated Loratadine F-MELT® ODTs were carried out for one week at RT (25°C) and 75% RH under open conditions. The tablets retained 87.81% of hardness and there was no drastic deviation with respect to pharmacopoeia or oral disintegration times (Table 4).

Table 4. Stability Test of solvent granulated (SG) Loratadine ODTs Formulation

	Initial	25°C, 75% RH, Open, 1 week
Tablet hardness (N)	47.6	41.8
Compression force (kgf)	290-330	-
Pharmacopoeia disintegration time (s)	11.13	9.18
Oral disintegration time ODT-101* (s)	13.38	15.00
Mouth feel	Good	-

*Equipment to measure ODTs (Toyama Sangyo Co., Ltd.)

TASTE MASKED FAMOTIDINE ODTs FORMULATION WITH F-MELT®, A SUCCESSFUL EXAMPLE WITH WATER GRANULATION



Taste masking is more necessary and important to success of ODTs products on the market. Available taste masking technologies include use of flavors and sweeteners, coating of drug particles with inert materials, formation of inclusion complexes, molecular complexes of drug with other chemicals, microencapsulation, multiple emulsions, prodrugs, liposomes, dispersion coating, and ion exchange resins. These technologies are not only used to mask the taste of drugs but also to enhance the bioavailability of drugs. Among these technologies, use of flavors and sweeteners is simpler, cost effective, and suitable with F-MELT®. Sweeteners and flavoring agents can be natural or synthetic such as peppermint, lemon oil, clove, balsam, stevia, aspartame, sucralose, neotame, acesulfame potassium, sucrose, sorbitol, xylitol, saccharin, and others. F-MELT® already contains xylitol which partly contributes to good taste of ODTs. Furthermore, depending on APIs, formulators can add other sweeteners and flavors in order to minimize the bitterness of APIs. Famotidine belongs to a group of drugs called histamine (H₂) blockers. It works by decreasing the amount of acid that stomach produces. Famotidine is bitter in taste and need taste masking in order to be acceptable to patients who suffer from ulcers in the stomach or intestines.

Water granulation of Famotidine was carried out with a portion of F-MELT® Type M (ratio 2:5). The granules were passed through No.25 sieve (710 μ m) and dried overnight at 55°C. The dried granules were further passed through a No.60 sieve (250 μ m) and blended with additional F-MELT® Type M, taste masking agents and lubricant to prepare ODTs. Addition of 0.4% sucralose, 0.4% acesulfame potassium and 0.05% micronized menthol could eliminate the bitter taste of Famotidine. The ODTs showed sufficient hardness (approx. 50N) and a disintegration time of less than 30s (Table 5). Dissolution was almost 100% (Fig 3). Dry blending and direct compression of Famotidine with same amount of F-MELT® type M resulted in poor content uniformity and dissolution (data not shown).

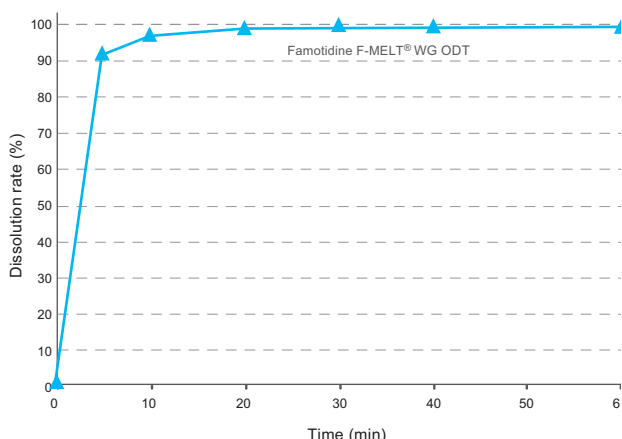


Table 5. Famotidine ODTs Formulation with F-MELT® Type M

Formulation	
Water-granulated Famotidine with F-MELT® Type M (2:5)	70 mg
F-MELT® Type M	127.5 mg
Sucralose	0.8 mg
Acesulfame potassium	0.8 mg
Micronized menthol	0.1 mg
Magnesium stearate	0.8 mg
Total	200 mg

Tablet Characteristics	
Tablet hardness (N)	47.0
Pharmacopoeia disintegration time (s)	13.49
Oral Disintegration time ODT-101*(s)	25.19

Tablet condition: Φ 8 mm, 200 mg/Tab, Rotary tableting machine
 *Equipment to measure ODTs (Toyama Sangyo Co., Ltd.)

Figure 3. Dissolution Profile of water granulated (WG) Famotidine ODTs Formulation

Dissolution was carried out with distilled water 900 ml, 37°C, paddle speed 50 rpm.

Stability tests of water granulated Famotidine F-MELT® ODTs were carried out for one week at RT (25°C) and 75% RH under open conditions. The tablets retained 98.29% of tablet hardness and there was no drastic deviation with respect to pharmacopoeia or oral disintegration times (Table 6).

Table 6. Stability Test of water granulated (WG) Famotidine ODTs Formulation

Characteristics	Initial	25°C, 75% RH, Open, 1 week
Tablet hardness (N)	47.0	46.2
Compression force (kgf)	330-360	-
Pharmacopoeia disintegration time (s)	13.49	10.64
Oral disintegration time ODT-101* (s)	25.19	20.21
Mouth feel	Good	-

*Equipment to measure ODTs (Toyama Sangyo Co., Ltd.)

SUMMARY

Wet granulation as a strategy to manufacture ODTs of poorly water soluble drugs proved to be a success with Loratadine and Famotidine ODTs. Wet granulation achieved overall quality of ODTs with respect to tablet hardness, disintegration time and dissolution profile. Taste masking of Famotidine was achieved by simple blending of flavors and sweeteners with F-MELT® Type M. In conclusion, wet granulation with F-MELT® could be an excellent approach to produce ODTs of poorly water soluble drugs which are fine powders.

REFERENCES

1. Bill Martineau 2009. A look at Fast-dissolving drug delivery system. Drug Delivery Technology. 36-38
2. FDA, Guidance for Industry: Orally disintegrating tablets (Rockville, MD, Dec. 2008) Eng. 18, 163-168.

PHARMACOPOEIA & REGULATORY

Type C meet all requirements of the current USP/NF, JP and EP
 US DMF Type IV filed in January 2007 # 20084

Type M meets all requirement of the current USP/NF, JP

PATENTS

Japan Patent No.3841804 August 18, 2006.

Patented in Japan, India, USA and China. Patent pending in Korea and EU.

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