

# Specialized Techniques for Developing ODT Dosage Forms

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Orally disintegrating tablets (ODTs) are unique dosage forms that facilitate improved patient convenience and compliance. However, they also come with unique formulation and manufacturing challenges, requiring specialised expertise, in order to create a product that appeals to customers while improving on disintegration and dissolution rates. Eurand employs a proprietary external lubrication tableting system to manufacture its AdvaTab® ODT. This is often used in combination with its Microcaps® technology for masking the bitter drug taste and rapidly dispersing microgranule technology. In this article, Dr Michelle Papp, Formulation Scientist, Dr Gopi Venkatesh, R&D Director, and Troy Harmon, Vice-President Business Development, all of Eurand, describe how, by removing lubricants from within the tablet formulation, an AdvaTab ODT provides important patient advantages through increased dissolution and disintegration rates. External lubrication also creates manufacturing advantages for partners, such as decreased overall production time and harder, more robust tablets that can be packaged in bottles or blisters. Eurand's recent commercialised AdvaTab products include Lamictal® ODT with GlaxoSmithKline and Unisom® SleepMelts with Chattem.

Tablets are still the pharmaceutical dosage form of choice for oral administration. During their manufacture, an extensive amount of friction between the tablet and the surfaces of the die and punch is generated as the tablet is ejected. This can impart considerable amounts of strain and shear to a tablet resulting in tablet defects such as sticking, capping and lamination.<sup>1-3</sup>

The tablet defects arising as a consequence of these adhesion and frictional forces are generally reduced by the incorporation of a hydrophobic lubricant such as magnesium stearate, stearic acid, or sodium stearyl fumarate (Pruv®) in the final blending step prior to tableting. However, this internal lubrication process imparts a hydrophobic film on the surface of the powdered or granulated formulation which can negatively impact the performance properties of the resultant tablets.

Depending on the formulation, choice of lubricant and its concentration, this method may result in a longer disintegration time (DT) and slower dissolution due to reduced water penetration rate, as well as lower tablet strengths due to decreased interparticulate bonding. These negative effects from internally incorporated lubricants can become problematic, especially in the case of orally

disintegrating tablets, which are required to disintegrate within 30 seconds when tested for DT by United States Pharmacopeia (USP) Disintegration Test Method <701>.

To reduce the negative aspects, a new approach has been developed that localises the application of lubricants to the interface between tablet and tooling. This method is known as external lubrication.

There are different techniques for applying an external lubricant during tableting. Manual application methods, such as gentle blending of the tooling with the powdered lubricant<sup>4</sup> or swabbing the lubricant in suspension onto the punches and die wall<sup>5</sup>, have long been known and are still used in compaction studies utilising a single station tablet press or a compaction simulator. Although useful for small-scale studies, this method is not practical for production scale. Therefore, a second automated method involves the direct application of lubricant powders to tooling on rotary presses. Recent demonstrations<sup>5-16</sup> highlighting the advantages of external lubrication by automated systems have stimulated interest in its use and a variety of equipment is available.

Kyowa Hakko Kogyo (Tokyo, Japan) has developed a powder material spraying device



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for use in combination with an industrial-scale rotary tablet press called the ExLub system. It is extensively used by both Kyowa Hakko Kogyo and Eurand for the development and commercialisation of several ODT products.

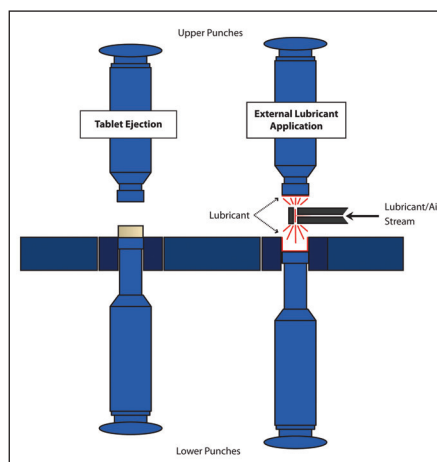
A second system, the Fette Tablet Press-PKB-1 (Press-Kammer-Beschichtung) external lubrication system manufactured by Fette GmbH (Schwarzenbek, Germany), was first described by Gruber *et al.*<sup>6</sup> Currently, PKB-1, -2, and -3 external lubrication systems are available from Fette and magnesium stearate and sodium stearyl fumarate as external lubricants on this system have been evaluated.<sup>6,10</sup>

A Kikusui (Yokohama, Japan) tablet press equipped with an external lubrication system, ELS-P1 or P2<sup>14,15,16</sup> has also been described in the literature for the external application of magnesium stearate. Other external lubrication systems<sup>17,18,19</sup> exist, such as Die Wall Lubrication System and Punch Face Lubrication System offered by GEA Pharma Systems (Courtoy; Halle, Belgium) and Lubrication System offered by Sejong Pharmatech Co Limited (Incheon, South Korea), which uses a US FDA-approved edible oil as the lubricant. However these are not described in the literature. Bayer Aktiengesellschaft (Leverkusen, Germany) has an approved US patent (US6,079,968) for an external lubrication system.

The above external lubrication systems involve the spraying of the lubricant by an air nozzle directly onto a tablet tooling similar to that represented in figure 1. However, the individual systems differ in the details of achieving/monitoring the lubricant spray rate and its adherence to the punches and die wall. For example, the ExLub system has a penetrating aperture and a dispersion chamber with a pulsating vibration air supply to control the spray rate precisely. For the ELS-P1 or ELS-P2 the use of the electrostatic charge function on the spray nozzle improves the adherence and hence increases the amount of the lubricant deposited on the punch surfaces and die wall.

In all cases, these external lubrication methods concentrate the lubricant at the interface between the formulation and the stainless steel tooling where friction is at a maximum. The main advantage is that it leaves the powder surfaces on the interior of the tablet lubricant free.

With traditional dry-blended lubricants, the surface morphology of the excipients can become hydrophobic<sup>3</sup> potentially compromising the strength of the compacts. This necessitates additional energy, in the form of higher compaction forces, in order to fracture lubricated particles to create the clean,



**Figure 1: Schematic of external lubrication system showing lubricant application to tablet tooling system surface**

unlubricated surfaces needed for the formation of strong intermolecular bonds.

With external lubrication, lubricants are not coating the particles to be compressed, instead the lubricant is directed to the tooling. Therefore the generation of new surfaces is not necessary. External lubrication methods require less force to produce tablets of comparable strength, in contrast to those formulated with internal lubricants.<sup>4,5</sup> In some cases, tablets are 10-30% stronger at comparable compression forces when external lubrication is employed.<sup>4</sup>

Surprisingly, the increased tablet strengths associated with externally lubricated tablets, compared with internal lubricants, does not result in an increased disintegration time nor

decreased dissolution. The use of an external lubricant for the tableting of calcium hydrogen phosphate/starch granules showed a 20-second faster dissolution compared with the same granules blended with magnesium stearate.<sup>6</sup>

Otsuka *et al* reported the immediate release of trypsin (100% in approximately seven minutes) when tableted using external lubrication, compared with less than 20% release of the drug in 20 minutes when an internal lubricant was used. In this case, the disintegration of the external lubricated tablets was immediate whereas the internally lubricated tablets failed to disintegrate.<sup>4</sup> This was attributed to the external lubricant method producing a tablet with higher porosity and increased wettability.

The advantage of increased dissolution and disintegration without impacting negatively on tablet strength makes external lubrication an ideal choice for ODT development. Figure 2 provides a summary of ODT products manufactured by Eurand for commercialisation or to support phase III clinical development.

All of these products take advantage of the benefits provided by utilising external lubrication in their manufacture. For example, diphenhydramine HCl, an antihistamine, the active ingredient in the OTC brand product, Unisom<sup>®</sup> is indicated to induce sleep, typically taken at bedtime. The ODT product comprising Diffucaps<sup>®</sup> beads taste-masked using Eurand's Microcaps<sup>®</sup> technology, AdvaTab<sup>®</sup> microgranules (rapidly dispersing microgranules), shows superior oral disintegration results as well as better taste/flavour results, while providing a robust dosage form.

Although it is desirable to optimise and control the quantity of the lubricant sprayed onto die wall and punch surfaces during the production of such ODTs, Jahn and Steffens, and Yamamura *et al*, make the following observations regarding such:

- Lubricant spray rate is optimised by determining the threshold lubricant concentration on the tablet or the spray rate that is characterised by the lowest ejection force observed during tablet ejection.<sup>9</sup>
- Higher spray rates above the optimised level had no significant enhancement but lubricant concentration on the tablet continued to increase.<sup>9</sup>
- Based on the compaction data for lactose, mannitol, sorbitol and pregelatinised starch, a nearly linear dependency between spray rate and lubricant (magnesium stearate) concentration of tablet was evident.<sup>9</sup>

ODT Product <sup>20-24</sup>	Available Strengths	Corresponding Tablet Diameter and Weight*
Lamictal <sup>®</sup> ODT	25 mg	7.0 mm, 100 mg
	50 mg	9.0 mm, 200 mg
	100 mg	11.0 mm, 400 mg
	200 mg	14.0 mm, 800 mg
Temazepam ODT	7.5 mg	7.0 mm, 125 mg
	15 mg	9.0 mm, 250 mg
	22.5 mg	10.0 mm, 375 mg
	30 mg	11.0 mm, 500 mg
Undisclosed ODT	25 mg	9 mm, 250 mg
	50 mg	11 mm, 500 mg
	75 mg	13 mm, 750 mg
Paracetamol ODT	250 mg	13 mm, 700 mg
	500 mg	17 mm, 1400 mg
Ranitidine HCl ODT	150 mg	15 mm, 1100 mg
	75 mg	11 mm, 550 mg
APAP/HCB ODT	300/10 mg	15 mm, 1100 mg
	500/5 mg	17 mm, 1400 mg
Unisom <sup>®</sup> (Diphenhydramine HCl ODT)	25 mg	11 mm, 450 mg
Undisclosed ODT CR	10 mg	8.0 mm, 200 mg
	25 mg	12.0 mm, 500 mg
	50 mg	15.0 mm, 1000 mg

**Figure 2: Summary table of products using Eurand's AdvaTab<sup>®</sup> technology**

- Tensile strength has been observed to be nearly constant, despite the lubricant concentration increased up to ten-fold from 0.12% to 1.27%<sup>9</sup> in contrast with conventional internal lubrication, where variations in the lubricant concentration or modifications in the blending dynamics of the lubricant prior to compression cause significant variations in the resultant tablet tensile strengths, thereby necessitating continued optimisation whenever the blending dynamics of the lubricant change due to changes in the composition, equipment, or both.
- Evaluation by scanning electron microscope (SEM) observation by focused ion beam showed the thickness of the magnesium stearate layer on the central part of the tablets be relatively uniform and thinner than at the edges for two different spray rates.<sup>16</sup>

As an added benefit, external lubrication has been shown to increase the stability of certain APIs, such as those that are incompatible with magnesium stearate. Eprazinone hydrochloride is one such compound. Compressed tablets of eprazinone hydrochloride with 0.12% external magnesium stearate had a higher percentage of the API remaining after four weeks at 40°C and 75% RH compared with the internally lubricated formulation containing 1.06% magnesium stearate. The lower amount of magnesium stearate required by the formulation utilising external lubrication resulted in the increased stability of eprazinone hydrochloride.<sup>16</sup>

Increased stability of the enzymatic drug trypsin has also been reported from an external lubrication technique.<sup>1</sup> In this case, the lower compression forces required to produce a tablet of corresponding strength to that of internally included magnesium stearate resulted in exposing the API to less heat or pressure. As a result, less loss of activity of the API was reported.

## CONCLUSION

Although the advantage of a stronger tablet with faster dissolution and disintegration times might not be obvious for a conventional tablet, it can provide a critical advantage in the development of orally disintegrating tablets. Likewise, utilisation of this technology can eliminate an additional manufacturing step, decreasing the overall production time.

Taken as a whole, external lubrication techniques can provide many benefits over traditional tablet manufacturing methods that incorporate a lubricant in the blend.

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