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WHY ORAL DISINTEGRATING TABLETS?

In this piece, Carmen Popescu, PhD, Senior Project Coordinator, Roquette, provides an overview of the Orally Disintegrating Tablet (ODT) landscape, describing how these dosage forms can be used to improve and differentiate drug products, different manufacturing methods and how this class of oral delivery system might be applied in the future.

Oral Disintegrating Tablets (ODTs) are patient-centric drug delivery systems (for example, for paediatrics, geriatrics, and psychiatric patients with dysphagia) designed to increase patient compliance. ODTs are preferred to classic dosage forms (swallowable / chewable / suckable tablets) due to ease of administration (portability, “on the go”) without water, pleasant taste and mouth-feel – more of “a treat” than a

“Recently, the US FDA approved SPRITAM (levetiracetem) ODT tablets produced by 3D printing. This is a significant step towards personalised drug delivery.”

treatment. Reduced first-pass metabolism, faster onset of action, better absorption and, in turn, improved bioavailability are their very appealing benefits. Manufacturers’ attraction for these dosage forms resides in improved lifecycle management, market differentiation, innovation and brand creation. Moreover, in recent years, we can see their remarkable expansion from Rx to OTC, nutraceuticals (vitamins, minerals, etc) and biologics. In response to

the increased popularity of ODTs on the market, the excipients industry created ready-to-use platforms in order to ease the formulation process.

WHAT ARE THE MAIN REQUIREMENTS FOR AN ODT?

As per the US and EU pharmacopoeias, an ODT has to weigh 500 mg (EP, USP) or less, disintegrate in 2 mL available saliva in less than 30 seconds (USP) or 180 seconds (EP) and the friability is to be $\leq 1\%$ (EU, USP).^{1,2,3}

In order to satisfy these requirements, the filler has to create a porous matrix in which the 2 mL saliva will be fast-channelled to the super disintegrant in order to break down within 30 seconds (Figure 1). Mannitol is the chosen filler (but there are other candidates like dextrose, lactose, starch, etc) due to it being water soluble but not hygroscopic (reduce interaction with the water penetration through the matrix pores) and protects actives stability.

WHAT PROCESSES ARE AVAILABLE TO MANUFACTURE ODTs?

Freeze-drying, spray-drying, direct compression, molding sublimation, mass extrusion, and cotton candy are the commonly used methods in the industry. Amongst these, direct compression is the



Dr Carmen Popescu
Senior Project Coordinator
T: +1 630 463 9436
E: carmen.popescu@roquette.com

Roquette America, Inc
2211 Innovation Drive
Geneva, IL 60134
United States

www.roquette.com

most cost-effective and easy-to-handle on standard equipment, resulting in low-friability tablets.

In recent years, the excipients industry has developed a number of ready-to-use ODT platforms by co-processing the filler, usually mannitol, with a superdisintegrant. The platforms include:

- F-MELT® (Fuji Chemical Industries, Tokyo, Japan)
- Ludiflash® (BASF, Ludwigshafen, Germany)
- Parteck® ODT (Merck Millipore, Billerica, MA, US)
- Pearlitol® Flash (Roquette Pharma, Lestrem, France)
- Pharmaburst® (Catalent, Somerset, NJ, US)
- PROSOLV® ODT (JRS Pharma, Rosenberg, Germany)

The main challenge in ODT formulation is the excipients screening in order to find the right balance between disintegration time, friability, API stability and mouth feel. These aspects are explored in greater detail in the case studies that follow.

CASE STUDY 1

Disintegration-Time Optimisation of Ready-to-Use Platforms

Disintegration time can be evaluated *in vitro* as per the USP/EU Pharmacopoeias' methods or any method using Texture Analyzer and their correlation with *in vivo* evaluation by a taste panel (Figure 2).

300 mg ODT placebos were made using ready-to-use ODT platforms at two hardness values (50 N and 90 N) and their disintegration times were evaluated *in vitro* (Figure 3a & b) and *in vivo* (Figure 3c).

ODT platforms composition filler: disintegrant is as follows: P1 (Mannitol: Starch); P2 (Mannitol: Crospovidone, PVA, PVP, SLS); P3 (Mannitol: Crospovidone, MCC, SiO₂, Fructose) and P4 (Mannitol: Croscarmellose).

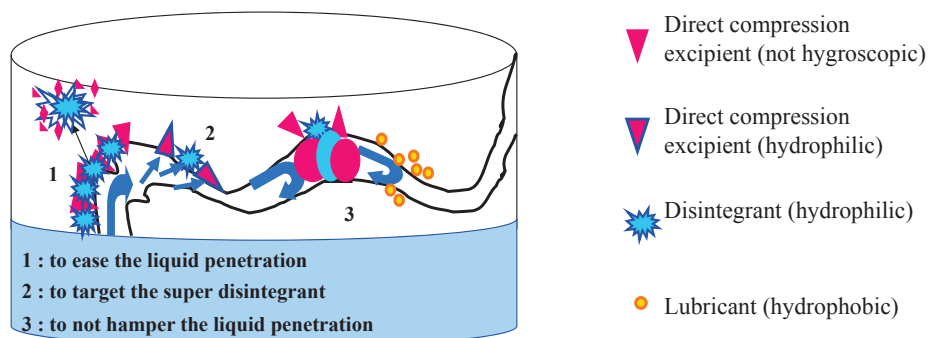


Figure 1: Mechanisms of ODT disintegration.

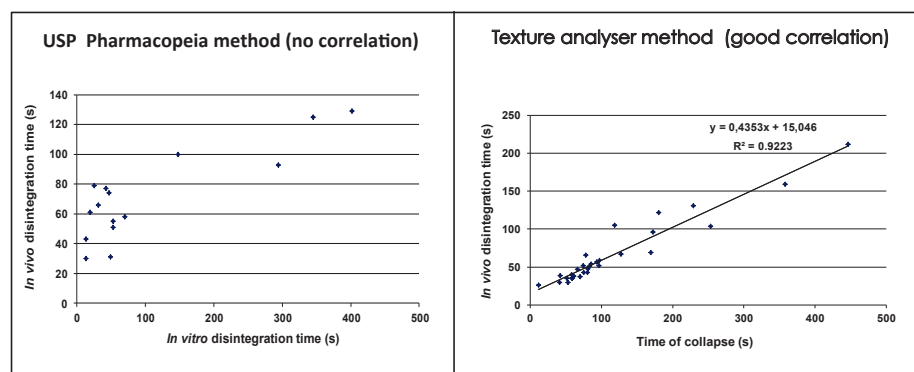


Figure 2 Disintegration time in vitro/in vivo correlation.

Tablet hardness has no effect on the disintegration time *in vitro* (both methods Figure 3a and Figure 3b) or *in vivo* (Figure 3c) for P1 while for the other platforms there is noticeable variation as a function of hardness. The reason for P1's short disintegration time resides in the water access (through porous matrix) to the disintegrant due to its superior wettability compared with the other platforms (Figure 4).

CASE STUDY 2

Impact of ODT Platform Composition on Mouth-Feel

24-trained panelists were asked to put an ODT placebo between tongue and palate applying a slight pressure and then their opinion about the mouthfeel was

recorded. Mouth-feel is critical in patient acceptance of an ODT (due to its residence time in the buccal area) and is very much linked to attributes such as smooth, creamy, sweet, etc. Unfortunately, for some ODT platforms, the synthetic origin of their components seems to affect their taste and texture negatively. The taste panel evaluation of P1 to P4 commercially available ODT platforms were as follows:

- P1: Sweet taste, creamy, smooth and fine texture and off notes (Medicinal)
- P2: Creamy and sticky texture and off notes (Dry, Glue, Cardboard, Bitter)
- P3: Not very sweet, takes too long time to melt and off notes (Cardboard, Bitter)
- P4: Takes too long to melt, hard center and off notes (Cardboard, Chemical)

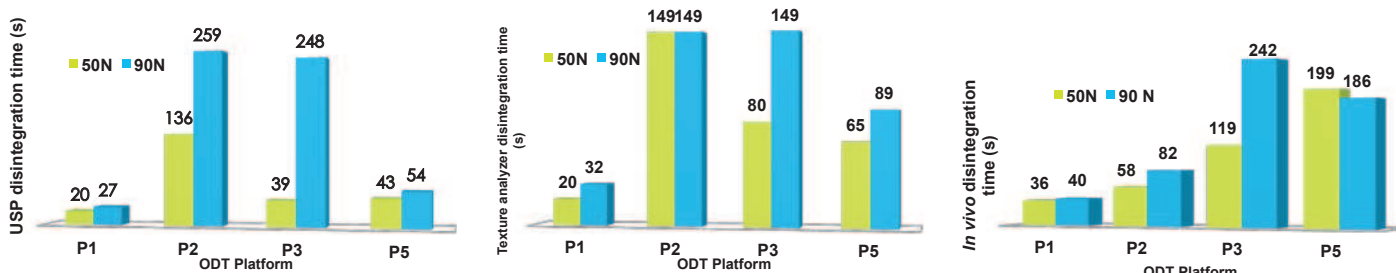


Figure 3: Disintegration times (a) in vitro, using the USP method, (b) in vitro using Texture analyzer method, and (c) in vivo.

CASE STUDY 3

Impact of ODT Platform Composition on Chemical & Physical Stability

ODTs were formulated with 6% benzocaine (as a model drug), 1.5% magnesium stearate, and 92.5% of the respective P1, P2, P3 ODT platforms (as described previously) and P4 (mannitol: xylitol, MCC, crospovidone, Mg alumino silicate, DCP). Each formulation was tableted at 500 mg weight using 10 mm diameter concave punches on a Korsch XP1 research tableting machine under two conditions.

The tablets in the first set were produced at different compression force depending on platform compressibility to create tablets with an average hardness of 100 N. The tablets in the second set were made under a constant compression force of 20 kN, which resulted in tablets with varying hardness. Tablets were evaluated in accordance with US Pharmacopoeia methods for hardness, friability, and *in vitro* disintegration time. Tablets were placed under ICH stability conditions in humidity chambers at 25°C/60% RH or under accelerated conditions, 40°C/75% RH, for up to six months in open pans. Following storage under the various stability conditions, tablets were photographed and their diameter measured. Benzocaine was chosen as a model drug due to its

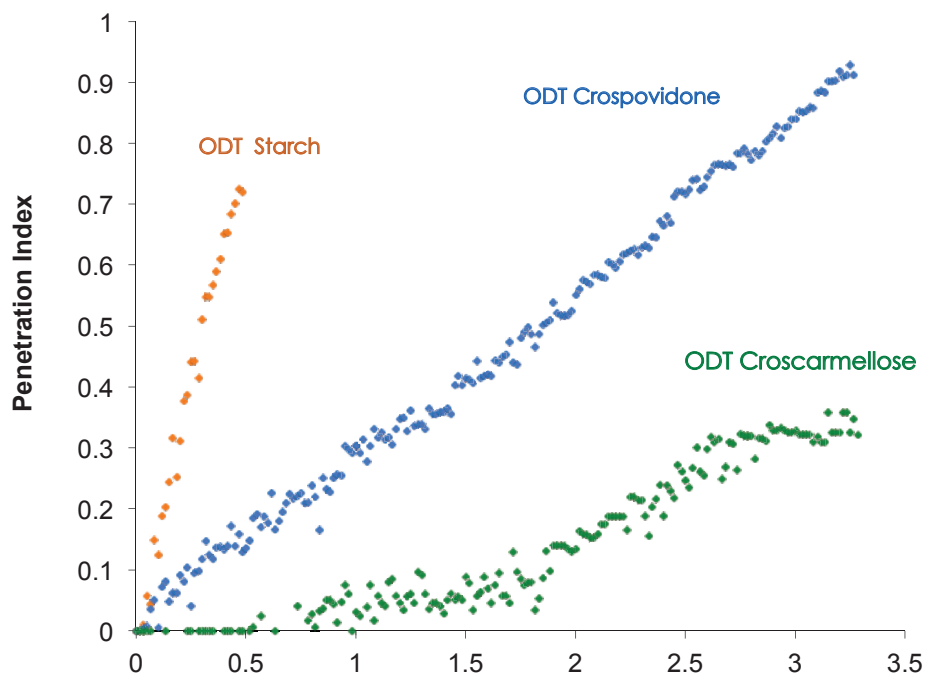


Figure 4: Wettability of ODT platforms with differing disintegrants (P1 has the fastest disintegration due to highest disintegrant wettability).

propensity (H2N group) to degrade under certain circumstances (reducing sugars, formic acid, and formaldehyde) and its degradation (Brown Millard reaction, N- Formyl benzocaine, p-amino benzoic acid, amide degradation product) under stability conditions was evaluated by LCMS.

Physical stability was impacted by

reducing sugar (fructose), superdisintegrants and MCC (see Figure 5), while chemical stability was impaired by reducing sugar (fructose) and reactive residues (peroxides, formic acid and formaldehyde) in crospovidone, PVP or PVA. P1 and P2 displayed a very good chemical and physical stability.⁴

Benzocaine ODT formulations	Day 0		Day 90		Day 180	
			25°C/60% RH		40°C/75% RH	
	100 N	20 kN	100 N	20 kN	100 N	20 kN
Mannitol Maize starch P1						
Mannitol Crospovidone PVP PVA SLS P2						
Mannitol Crospovidone MCC SiO ₂ Fructose P3						
Mannitol Xylitol MCC/Crospovidone Mg alumino silicate DCP P4						

Figure 5: Benzocaine stability study results.

ODT BY 3D PRINTING: A TRANSITION TO PERSONALISED MEDICINE

Recently, the US FDA approved SPRITAM (levetiracetam) ODT tablets produced by 3D printing. This is a significant step towards personalised drug delivery being tailored to the individual patients based on their predicted response or risk of disease. The treatment will be more cost-effective and accurate or, in other words, “therapy with the right drug at the right dose in the right patient”.⁵

GIVING PRACTICALITY TO NOVELTY

It is well known that more than 45% of new drug entities have solubility issues, and micronisation/ nanonisation is one way to address this problem. However, reducing the particle size at the micro/ nano scale, the drug is usually delivered only as an injectable. Normally it cannot be formulated as a conventional tablet because, during compression, particles will aggregate resulting in bigger particle size

and solubility reduction. However, in the case of ODTs, due to low compression force applied, the particle size is not changed.

For the same reasons, ODTs are potentially very suitable for protein and peptide delivery, preserving their structure, with delivery in the buccal cavity increasing their bioavailability. As the next generation of drugs coming through pipelines are increasingly biopharmaceuticals, ODT represents a viable option for their oral delivery.

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ABOUT THE AUTHOR

Dr Carmen Popescu holds a BS in Physics and a PhD in Biophysics from the University of Bucharest, Romania. She is a Senior Project Co-ordinator at Roquette America, Inc, and Adjunct Associate Professor with University of Illinois at Chicago, Roosevelt University, and the University of Tennessee. She has published more than 120 research papers, book chapters and presentations on classic and new drug delivery dosage forms for small and large molecules. Additionally she is a reviewer for the International Journal of Pharmaceutics, Journal of Pharmaceutical Sciences, European Journal of Pharmaceutics and Biopharmaceutics, Journal of Pharma & Pharmaceutical Science and an active member of AAPS and CRS.



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