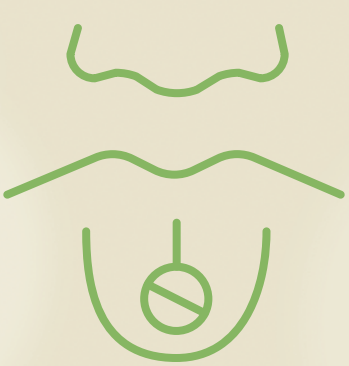
CUSTOMIZING ODT FORMULATIONS WITH THE RIGHT PARTNER



ORAL DISINTEGRATING TABLET SOLUTIONS

ROQUETTE
Offering the best of nature™

AN UNWAVERING COMMITMENT TO ENABLING
HEALTH-SUPPORTING NUTRACEUTICAL & OTC CONSUMER PRODUCTS

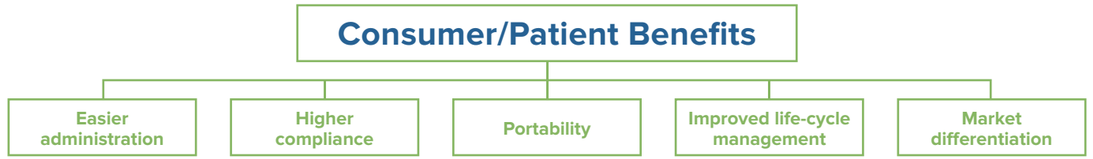
Improve consumer compliance by relying on Roquette's excipients to formulate stable, easy-to-administer Oral Disintegrating Tablets (ODT).

Pharmaceutical and nutraceutical formulators and manufacturers are continuously seeking to improve and simplify drug and nutritional supplement delivery. For many patients, such as pediatrics, geriatrics, and patients suffering from dysphagia, fast-dissolving dosage forms are the best option.

Designed to improve the quality, stability, and flexibility of your finished drug product as well as increase consumer compliance, Roquette has developed several versatile excipients and ready-to-use platforms for Oral Disintegrating Tablet (ODT) formulations.

THE PREFERRED FORMULATION FOR EASE OF ADMINISTRATION

Upon dissolving, ODT dispersion in the oral cavity facilitates pre-gastric absorption of drugs (buccal and pharyngeal cell uptake) and the avoidance of unwanted first-pass metabolism. Pre-gastric absorption reduces dosage requirements and is highly beneficial for drugs that undergo hepatic metabolism and drugs with active ingredients that produce toxic metabolites mediated by first-pass liver and gastric metabolism. The diagram below shows some of the patient benefits resulting from ODT delivery.



In recent years there has been a remarkable expansion of ODT formulations from prescription to OTC products, nutraceuticals (vitamins, minerals) and biologics.

ODT FORMULATION REQUIREMENTS

Per US and EU pharmacopeias, an ODT must weigh no more than 500 mg, disintegrate in 2.0 mL of available saliva in less than 30 seconds (USP) or 180 seconds (EU), with friability equal to or less than 1.0%.

Property	Value	Reference
Weight (mg)	≤ 500	FDA[1]
Disintegration time (s)	≤ 30	FDA[1] USP[2]
	≤ 180	Ph. Eur.[3]
Friability (%)	≤ 1	USP[2], Ph. Eur.[3]

[1] Guidance for Industry FDA - 2008
[2] United States Pharmacopeia
[3] European Pharmacopeia 8.2 - 2014

Active ideal characteristics	Active unsuitable characteristics
Low dose	Short half-life and required frequent dosing
Small to moderate molecular weight	Very bitter or otherwise unacceptable taste because taste masking cannot be achieved
Stable in water and saliva	Requires controlled or sustained release
Partially non-ionized at the oral cavity pH	
Ability to diffuse and partition into the epithelium of the upper GI tract	
Ability to permeate oral mucosal tissue	

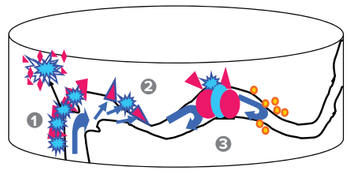
Manufacturing Processes

Freeze-drying, spray drying, molding sublimation, and mass extrusion are commonly used manufacturing methods for ODT formulations. However, direct compression is the most cost effective and favorable method, with the greatest ease of handling on standard equipment, resulting in low friability tablets.

ODT EXCIPIENT DYNAMICS

To satisfy these requirements, a filler must maximize the porous matrix in which the 2.0 mL of saliva will be fast-channeled to the super-disintegrant to facilitate break down within 30 seconds.

Due to its propensity of being water soluble but not hygroscopic while still protecting API stability, mannitol is the filler of choice for ODT formulations.



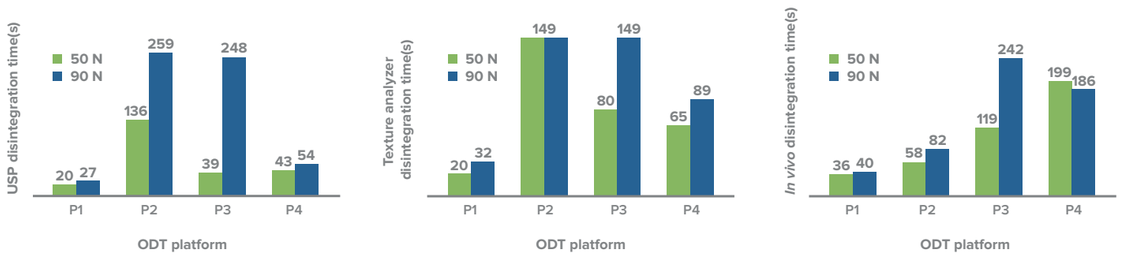
1. to ease the liquid penetration
2. to target the super disintegrant
3. to not hamper the liquid penetration

- Direct compression excipient (not hygroscopic)
- Direct compression excipient (hydrophilic)
- Disintegrant (hydrophilic)
- Lubricant (hydrophobic)

CASE STUDIES

Disintegration Time Optimization

To determine the effects of excipient addition on disintegration time, 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* (Figures 1a, 1b) and *in vivo* (Figure 1c).



P1 - PEARLITOL® Flash (Mannitol + Starch)
P2 - Mannitol + Crospovidone, MCC, SiO2, Fructose
P3 - Mannitol + Crospovidone, PVA, PVP, SLS
P4 - Mannitol + Croscarmellose

Figure 1: Disintegration times (a) *in vitro*, using the USP method, (b) *in vitro,* using Texture analyzer method, and (c) *in vivo*.

Tablet hardness showed no effect on the disintegration time *in vitro* (Figures 1a, 1b) or *in vivo* (Figure 1c) for P1, while the other platforms show a noticeable variation as a function of hardness. The reason for P1's short disintegration time resides in the water access (through the porous matrix) to the disintegrant, resulting from its superior wettability compared with the other platforms.

Bottom line
PEARLITOL® Flash (P1, co-processed mannitol and maize starch) is a ready-to-use solution offering superior wettability.

Enhancing Active Stability Using Commercially Available ODT Platforms

To determine the impact of ODT platform composition on chemical and physical stability, ODTs were formulated with 6.0% 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 aluminum silicate, DCP).

Figure 2: The impact of excipient addition and ODT platform composition on benzocaine formulation stability.

Each formulation was tableted at 500 mg weight using 10 mm diameter concave punches on a Korsch XP1 research tableting machine under two conditions:

- Different compression force depending on platform compressibility to create tablets with an average hardness of 100 N.
- 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.

Physical stability was impacted by reducing sugar (fructose), super-disintegrants and MCC, while chemical stability was impaired by reducing sugar (fructose) and reactive residues (peroxides, formic acid and formaldehyde) in crospovidone, PVP or PVA.

Bottom line
PEARLITOL® Flash (P1, co-processed mannitol and maize starch) is a ready-to-use solution offering enhanced chemical and physical stability.

EXCIPIENTS AND PLATFORMS FOR ODT

Brand Name	Excipient	Functionality	Pharma/Nutra	Direct compression/granulation	Comments
PEARLITOL® FLASH ODT PLATFORM	Mannitol co-processed with starch (ready-to-use filler)	Filler co-processed with disintegrant	+/-*	+/-	-API stabilizer -Direct compression filler -Imparts sweet taste, creamy mouth feel
STARLAC® ODT PLATFORM	Lactose co-processed with starch (ready-to-use filler)	Filler co-processed with disintegrant	+/-*	+/-	-API compatible with lactose -Direct compression filler -Imparts sweet taste, creamy mouth feel
PEARLITOL® 200SD	Mannitol + crospovidone (mixture)	Filler + superdisintegrant	+/+	+/+	-API stabilizer -Direct compression filler/granulation binder -Imparts sweet taste, creamy mouth feel
PEARLITOL® 200SD PLUS SOLUTAB®	Mannitol + croscarmellose (mixture)	Filler + disintegrant	+/+	+/+	-API stabilizer -Direct compression filler/granulation binder -Imparts sweet taste, creamy mouth feel
PEARLITOL® 200SD PLUS GLYCOLYS®/EXPLOSOL®	Mannitol + sodium starch glycolate (mixture)	Filler + disintegrant	+/+	+/+	-API stabilizer -Direct compression filler/granulation binder -Imparts sweet taste, creamy mouth feel

Brand name	Chemical name	Water content (%)	Particle size (mean diameter µm)	Bulk density	Tapped density	Compressibility index (%)	Flowability funnel (seconds)	Water solubility (g/100 mL, 20°C)	Hygroscopicity (Ph. Eur. 5.11)	Organoleptic properties	
										Sweetness (compared to sucrose)	Cooling effect
PEARLITOL® 200SD	Mannitol	<0.5	180	0.50	0.57	12	5	17	Non-hygropscopic	0.5	Low
PEARLITOL® FLASH	Co-processed mannitol and maize starch	<3.0	200	0.52	0.62	16	5.5	Contains 20% insoluble maize starch	Slightly hygropscopic	0.4	Low
STARLAC®	Co-processed lactose and maize starch	<3.0	125	0.57	0.68	16	4	Contains 15% insoluble maize starch	Slightly hygropscopic	2.0	None

*may not be applicable if starch in the nutra formulation is not desirable

LEARN MORE ABOUT ROQUETTE NUTRACEUTICALS & OTC SOLUTIONS

www.roquette.com | pharma@roquette.com

PH_NO_OVERVIEW-BR-01.1E/09.2018

ROQUETTE

Offering the best of nature™