

Introduction

Orally Disintegrating Tablets (ODTs) are fast gaining popularity as a novel oral drug delivery system. When placed in mouth, these tablets rapidly absorb the small quantity of available saliva and quickly disperse in about 10-45 sec.

ODTs demonstrate unique advantages by addressing patient compliance issues with pediatric, geriatric and uncooperative patients unable to swallow tablets. They also allow administration of medication without any need for water.

To-date a variety of ODTs with their own claim of advantages have been developed using technologies ranging from as simple as wet granulation or direct compression to as complex as lyophilization.

An ideal combination of excipients for ODTs should provide the following --

- Allow satisfactory drug loading and exhibit good moisture stability
- Mask bitter taste of drugs and offer an overall pleasant mouth feel
- Yield sufficiently robust tablets upon direct compression
- Enable rapid dispersion in the mouth without leaving any residue

No single excipient can fulfill the requirements of all ODT formulations. This study will assess the suitability of excipients and superdisintegrants for developing an ODT platform using conventional and non-conventional tests. This data may ultimately help in selection of the best possible combination of excipient and superdisintegrant for developing an optimal ODT formulation.

Experimental Methods

Tableting: DC placebo tablets (4mm thick) of Mannitol (Pearlitol®) DC, Sorbitol, SD Lactose, Microcrystalline Cellulose (MCC), Dicalcium Phosphate (DCP), and Pregelatinized Starch each containing 3% of either Glycolys® - sodium starch glycolate (SSG), Croscopovone or Croscarmellose as super-disintegrants were obtained on a Fette Exacta 21 with 16mm flat punches.

Tablet Analysis: Tablet hardness was measured using a Dr. Schleuniger Pharmatron Model 6D equipment. Tablet friability was measured using a VanKel friabilator. *In-vitro* tablet disintegration time (DT) was measured using the EP disintegration test. A panel of 9 people testing 3 tablets per day measured *in-vitro* DT and mouthfeel. Test results were scored using a standardized questionnaire.

Tablet Relaxation Kinetics: Tablets were placed in the cavity (24 mm diameter & 10mm depth) of an INSTRON universal extensometer. An initial force of 3N was applied to the surface using a 5mm diameter cylinder. 2 ml water was added and the time required to reduce the force to half its initial value (1.5N) was noted.

Tablet Wetting and Contact Angle: Measured by wicking evaluation carried out using a DIGIDROP GBX goniometer. Using a superfine needle, 1ml water (20°C) was dropped on the surface of the tablet from a distance of less than 1 mm from the tablet surface. The wetting and water penetration was measured by a high-speed camera (240 frames per second) at 0, 0.5, 1.5 & 3.5 sec with an accuracy of 5% for wetting angle and 0.3% for water penetration.

In-vitro DT of Placebo ODT Formulations

Table 1: Lubricant and Superdisintegrant Levels in Placebo Tablet Formulations

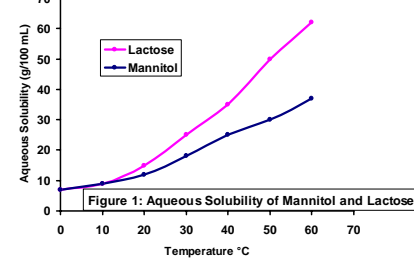
Bulk Excipient (qs)	Superdisintegrant*	Lubricant (Mg stearate)
DCP	3%	0.5%
Spray-dried Lactose	3%	0.6%
Mannitol DC (Pearlitol®)	3%	1.5%
MCC	3%	0.7%
Sorbitol	3%	0.7%
Pregelatinized Starch	3%	0.1%

*Croscopovone, Glycolys® and Croscarmellose used as superdisintegrants

Table 2: In-vitro DT & Tablet Friability with Various Excipients & Super-disintegrants

Bulk Excipient	In-vitro DT (seconds) / Friability (%)	
DCP	13 / 1.62	13 / 0.9
Spray-dried Lactose	49 / 1.42	53 / 1.52
Mannitol DC (Pearlitol®)	53 / 1.1	47 / 1.94
MCC	29 / 0.05	25 / 0.05
Sorbitol	148 / 1.52	345 / 0.7
Pregelatinized Starch	822 / 1.7	1061 / 0.7
	Croscopovone	Glycolys®
	Croscarmellose	

Mannitol and Lactose Exhibit Low Aqueous Solubility



Mannitol Particle Morphology & ODTs

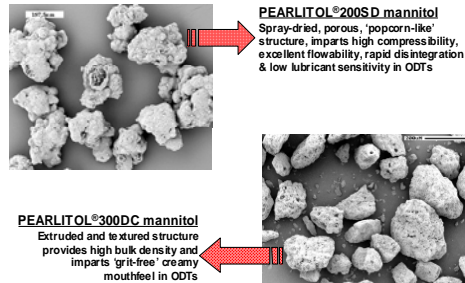


Figure 2: SEM Micrographs of Spray-dried and Extruded Pearlitol®

In-vitro DT - Discussion

Table 2 summarizes the *in-vitro* DT for various placebo ODT formulations. ODTs with friability < 2% were subjected to the *in-vitro* disintegration test.

ODTs containing Mannitol DC, Spray-dried lactose, DCP, and MCC exhibited a good *in-vitro* DT of less than 60 sec. Despite its low aqueous solubility (Fig. 1), Mannitol DC (Pearlitol®) allows rapid tablet dispersion by

- Imparting high porosity to tablets (Fig. 2)
- Allowing rapid water absorption by "wicking"

Sorbitol and pregelatinized starch tablets exhibited an *in-vitro* DT of >2 min.

Sorbitol tablets exhibit high hardness and low porosity, causing slow surface erosion of tablets due to solubilization and consequently a longer DT.

Pregelatinized starch by nature tends to absorb water and form a sticky layer at the tablet surface, which significantly reduces penetration of water into the core of the tablet, thus significantly increasing the DT.

ODT Formulations: In-vitro DT & Mouthfeel

Table 3: In-vitro DT with Various Excipients & Super-disintegrants

Bulk Excipient	In-vitro DT (seconds)		
DCP	30	61	43
Spray-dried Lactose	31	55	58
Mannitol DC	51	74	77
MCC	93	79	66
Sorbitol	100	125	129
Pregelatinized Starch	> 300	> 300	> 300
	Croscopovone	Glycolys®	Croscarmellose
	Superdisintegrants Used (each 3%)		

ODT formulations exhibited significantly different *in-vitro* vs. *in-vitro* DTs. Thus, pharmacopoeial disintegration tests may not serve as an accurate indicator of the *in-vitro* disintegration performance of ODTs.

The test panel also scored the palatability and mouth feel of various excipients.

- Mannitol DC and spray-dried lactose provided the best palatability & mouth feel
- MCC, DCP, and pregel starch provided chalky/starchy taste and gritty mouth feel
- Sorbitol, and pregelatinized starch, and sorbitol were not evaluated further due to their poor palatability, mouth feel or disintegration characteristics.

In-vitro In-vitro DT Ratio & Excipient Efficacy

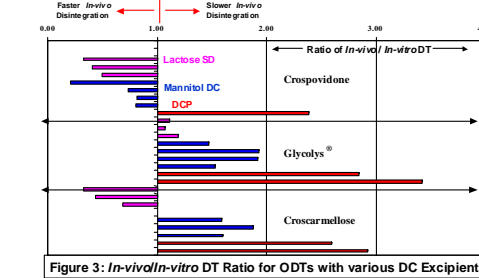


Figure 3: In-vitro In-vitro DT Ratio for ODTs with various DC Excipients

- Croscopovone exhibited a low *in-vitro*/*in-vitro* DT ratio signifying excellent *in-vitro* disintegration efficiency and was selected for further testing
- Among the bulk excipients, only Mannitol DC and spray-dried lactose were evaluated further due to their excellent palatability, mouthfeel and disintegration
- Glycolys® exhibits excellent disintegration in wet-granulated but not DC tablets

Tablet Relaxation Kinetics

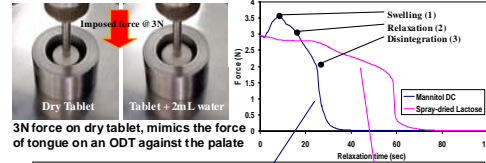


Figure 4: Relaxation Profiles for Mannitol and Lactose Tablets after Water Addition

Phase	Mannitol DC	Lactose SD
1. Swelling	Rapid pressure increase to 3.5N	No swelling of tablet
2. Relaxation	Rapid pressure fall below 3N	Prolonged relaxation phase
3. Disintegration	Rapid tablet dispersion (<30sec)	Slow tablet dispersion (60sec)

Rapid Relaxation kinetics of Mannitol enable fast dispersion of ODTs. Excipients exhibiting Rapid Relaxation are Ideal for use in Rapid Dispersing ODTs

Relaxation Kinetics & In-vitro DT Correlation

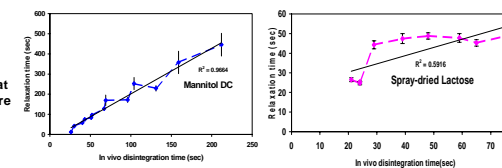


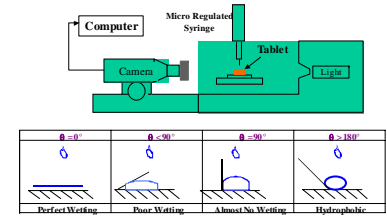
Figure 5: Correlation between Tablet Relaxation Profiles and In-vitro DT

Mannitol but not Lactose ODT exhibit good Relaxation time vs *in-vitro* DT correlation

Evaluation of *in-vitro* DT for an ODT formulation is generally a subjective process

For Mannitol ODTs, relaxation kinetics data may thus help in predicting *in-vitro* DT. Relaxation kinetics could also estimate changes in *in-vitro* DT over the shelf life

Wicking Test: Digidrop GBX Goniometer



Excipients Differ in their Wicking Abilities

Super-disintegrant	Bulk Excipient	Water Penetration (seconds) (Worst to Best)			
		0.0 sec	0.5 sec	1.5 sec	3.5 sec
None	Lactose	54 / -	37 / 0	31 / 0.4	19 / 0.6
	Mannitol	88 / -	85 / 0	78 / 0.1	71 / 0.2
	DCP	74 / -	65 / 0	57 / 0.3	47 / 0.4
Croscopovone	Lactose	50 / -	17 / 0.5	0 / 1	0 / 1
	Mannitol	87 / -	75 / 0.1	57 / 0.3	31 / 0.4
	DCP	50 / -	30 / 0	0 / 1	0 / 1
Croscarmellose	Lactose	43 / -	25 / 0.2	0 / 1	0 / 1
	Mannitol	95 / -	88 / 0	82 / 0.1	71 / 0.1
	DCP	84 / -	73 / 0.1	68 / 0.2	58 / 0.3
Glycolys®	Lactose	52 / -	27 / 0.5	7 / 0.8	0 / 1
	Mannitol	94 / -	84 / 0	74 / 0	57 / 0.2
	DCP	60 / -	43 / 0.1	19 / 0.8	15 / 0.9

Table 4: Water Penetration and Wetting Angles for Various ODT Formulations

Mannitol & Croscopovone The Best Overall ODT Combination

Table 5: Functionality scores for ODTs containing Croscopovone and various excipients

Bulk Excipient	Scores (5 = Best, 0 = Worst)					Overall Scores
	In-vitro DT	In-vitro In-vitro DT ratio	Relaxation	Wicking	Taste & Mouth feel	
DCP	4.5	0.5	3.5	3.0	1.5	13.0
SD Lactose	4.5	4.0	0.0	3.0	3.0	14.5
Mannitol DC (Pearlitol®)	4.0	4.5	4.5	2.5	4.5	20.0
MCC	3.0	*	(-2.0)	*	*	*
Sorbitol	2.5	*	(-1.5)	*	*	*
Pregel Starch	0.5	*	(-2.5)	*	*	*

* Not calculated due to poor mouth feel and/or disintegration characteristics of formulation

Rapid *in-vitro* ODT disintegration requires the low-volume solvent (saliva) to be available for interaction with the super-disintegrant rather than the bulk excipient.

A bulk excipient that absorbs majority of the saliva will divert it away from the super-disintegrant, thus reducing its swelling kinetics and increase tablet DT.

Compared to lactose and DCP, the lower affinity of mannitol for saliva, ensures optimal availability of saliva to interact with the super-disintegrant (= faster DT).

High excipient porosity and altering compression force ensures optimal wicking.

Tablet wetting can be improved by the addition of surface active wetting agents.

Summary and Conclusions

The existing *in-vitro* DT tests do not mimic *in-vitro* disintegration for a given ODT formulation as seen from the significant differences between *in-vitro* & *in-vitro* DTs

Mannitol DC and SD Lactose provide the best palatability & mouth feel to an ODT. MCC, DCP, and pregel starch impart a chalky/starchy taste and gritty mouth feel

Croscopovone exhibits a low *in-vitro*/*in-vitro* DT ratio signifying excellent *in-vitro* disintegration efficiency in a directly compressed ODT

Rapid Tablet Relaxation kinetics for Mannitol enable fast dispersion of ODTs with excellent correlation to the *in-vitro* DT. For Mannitol ODTs, relaxation kinetics data may thus help in predicting *in-vitro* DT

The porous nature of mannitol not only imparts high compressibility but also allows rapid uptake of water by "wicking", which results in faster disintegration

Low affinity of mannitol for saliva, ensures optimal availability of saliva to interact with the super-disintegrant, thus enabling the shortest DT

Combination of Mannitol DC (Pearlitol®) & Croscopovone provides the best directly compressed ODT with respect to palatability, mouthfeel & rapid disintegration