Screening and Identifying Optimal Combinations of Excipients and Super-disintegrants In the Development of Orally Disintegrating Tablet (ODT) Formulations

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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.

MATERIALS & 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), Crospovidone 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-vivo* DT andmouthfeel. 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 highspeed 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.

RESULTS & DISCUSSION

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%

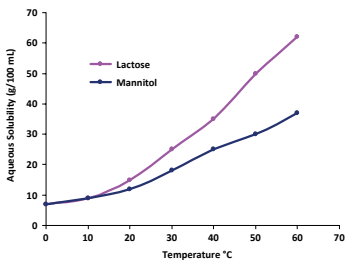
*Crospovidone, GLYCOLYS® and Croscarmellose used as superdisintegrants.

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

Bulk Excipient (qs)	*In-vitro* DT (seconds) / Friability (%)		
DCP	13 / 1.62	19 / 1.6	13 / 0.9
Spray-dried Lactose	49 / 1.42	53 / 1.52	70 / 0.8
Mannitol DC (PEARLITOL®)	53 / 1.1	47 / 1.94	42 / 0.92
MCC	29/ 0.05	25 / 0.05	31 / 0.21
Sorbitol	148 / 1.52	345 / 0.7	402 / 0.63
Pregelatinized Starch	822 / 1.7	1061 / 0.7	1060 / 1.55
	Crospovidone	**GLYCOLYS®**	**Croscarmellose**
	Superdisintegrants Used (3% each)		

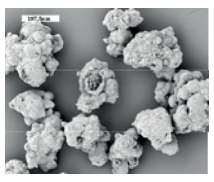
Mannitol and Lactose Exhibit Low Aqueous Solubility

Figure 1. Aqueous Solubility of Mannitol and Lactose.

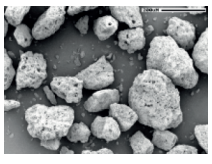


Mannitol Particle Morphology & ODTs

Figure 2. SEM Micrographs of Spray-dried and Extruded PEARLITOL®.



PEARLITOL®200SD mannitol
Spray-dried, porous, 'popcorn-like' structure, imparts high compressibility, excellent flowability, rapid disintegration & low lubricant sensitivity in ODTs.



PEARLITOL®300DC mannitol
Extruded and textured structure provides high bulk density and imparts 'grit-free' creamymouthfeel in ODTs.

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-vivo* DT & Mouthfeel

Table 3. *In-vivo* DT with Various Excipients & Super-disintegrants.

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

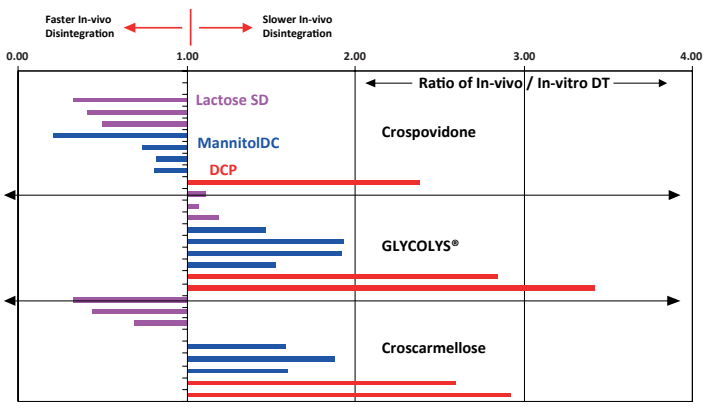
ODT formulations exhibited significantly different *in-vivo* vs. *in-vitro* DTs.
Thus, pharmacopoeial disintegration tests may not serve as an accurate indicator of the *in-vivo* disintegration performance of ODTs.
The test panel also scored the palatability and mouth feel of various excipients:

- 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,

MCC, DCP, pregelatinized starch, and sorbitol were not evaluated further due to their poor palatability, mouth feel or disintegration characteristics.

In-vivo/*In-vitro* DT Ratio & Excipient Efficacy

Figure 3. *In-vivo*/*In-vitro* DT Ratio for ODTs with various DC Excipients.

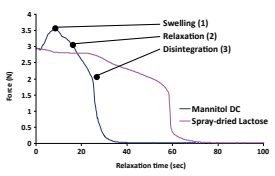


- Crospovidone exhibited a low *in-vivo*/*in-vitro* DT ratio signifying excellent *in-vivo* disintegration efficiency and was selected for further testing,
- Among the bulk excipients, only Mannitol DC and spray-dried lactose were evaluated further due to their excellent palatability, mouthfeel and disintegration,
- 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.

3N force on dry tablet, mimics the force of tongue on an ODT against the palate.



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)

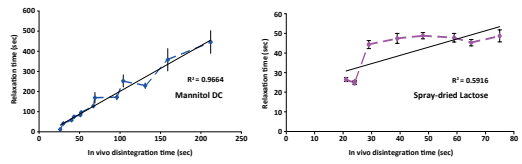
TIME

*After Water Addition.

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

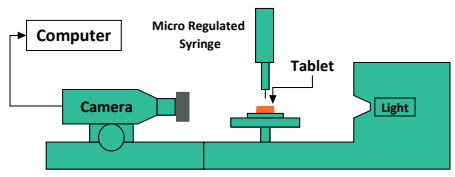
Relaxation Kinetics & *In-vivo* DT Prediction

Figure 5. Correlation between Tablet Relaxation Profiles and *In-vivo* DT.



Mannitol but not Lactose ODT exhibit good Relaxation time vs *in-vivo* DT correlation.
Evaluation of *in-vivo* DT for a ODT formulation is generally a subjective process.
For Mannitol ODTs, relaxation kinetics data may thus help in predicting *in-vivo* DT.
Relaxation kinetics could also estimate changes in *in-vivo* DT over the shelf life.

Wicking Test: Digidrop GBX Goniometer



θ = 0°	θ < 90°	θ = 90°	θ > 180°
Perfect Wetting	Poor Wetting	Almost No Wetting	Hydrophobic

Excipients Differ in their Wicking Abilities

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

WP = Water penetration (0=Worst, 1=Best)
θ° = Wetting angle

Super-disintegrant	Bulk Excipient	0.0 sec θ° / WP	0.5 sec θ° / WP	1.5 sec θ° / WP	3.5 sec θ° / WP
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
Crospovidone	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
GLYCOLYS®	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
Croscarmellose	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

Mannitol & Crospovidone The Best Overall ODT Combination

Table 5. Functionality scores for ODTs containing Crospovidone and various excipients.

Bulk Excipient	Scores (5 = Best, 0 = Worst)					Overall Scores
	In-vivo DT	*In-vivo*/*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-vivo* 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.

CONCLUSION

The existing *in-vitro* DT tests do not mimic *in-vivo* disintegration for a given ODT formulation as seen from the significant differences between *in-vitro* & *in-vivo* 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. Crospovidone exhibits a low *in-vivo*/*in-vitro* DT ratio signifying excellent *in-vivo* disintegration efficiency in a directly compressed ODT. Rapid Tablet Relaxation kinetics for Mannitol enable fast dispersion of ODTs with excellent correlation to the *in-vivo* DT. For Mannitol ODTs, relaxation kinetics data may thus help in predicting *in-vivo* 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®) & Crospovidone provides the best directly compressed ODT with respect to palatability, mouthfeel & rapid disintegration.