TECHNICAL INFORMATION

Application of **PROSOLV® ODT G2** in the Formulation of Ondansetron Orally – Disintegrating Tablets

Abstract

PROSOLV® ODT G2 was successfully used to formulate Ondansetron Oro-Dispersible Tablets (ODTs) of 4 and 8 mg strength. In a second step, **VIVAPHARM® PVPP XL10** was added to the formulation in order to optimize the disintegration performance. Comparison of these tablets to marketed generic ondansetron ODTs showed equivalent physical properties and disintegration times. **PROSOLV® ODT G2** offered an efficient and very straightforward way to produce Ondansetron ODTs by direct compression.

Introduction

Orally Disintegrating Tablets (ODTs) are becoming more popular with doctors and patients due to the advantages they offer over traditional tablets and capsules. ODTs dissolve quickly on the tongue with no water required. They can be taken virtually anywhere and offer discrete administration, broad application and are suitable for numerous indications and patient types.
ODT medications help improve compliance for younger and older patients and those patients who have general issues with dysphagia and are unable to swallow efficiently. Besides improving compliance and drug delivery, this technology can be used by companies to extend their current product life cycle.
Ondansetron is a drug that is used to prevent vomiting and nausea induced by cancer treatments and post-surgery. It is available in traditional tablets, orally disintegrating tablets (ODTs), films and liquids. The need for quick onset and aversion to swallowing or eating, makes ODTs a very attractive dosage form for this indication. There are numerous Ondansetron ODTs commercially available that are produced either by lyophilization or by traditional tablet manufacture.
For the purpose of this study, a generic ODT produced by standard tableting production was used as a reference. Prototype Ondansetron formulations, 4 mg and 8 mg, were developed using the **PROSOLV® ODT G2** orally disintegrating excipient matrix.

Reference product

The generic ODT contained aspartame, calcium stearate, colloidal silicon dioxide, mannitol, microcrystalline cellulose, polacrilin potassium, sodium starch glycolate, strawberry flavor, and talc. Additional product information is listed in table 1 below:

Reference Dose	Tablet Weight [mg]	Tablet Diameter [mm]	Tablet Hardness [N]	Disintegration Time [s]
4 mg	70	6	18.6	12
8 mg	140	7	48.1	17

Tab. 1 Reference Tablet Physical Data

One critical characteristic for ODTs is a rapid disintegration time, specifically less than 30 seconds. Tablets for the reference products had disintegration times of 12 and 17 seconds and respectable hardness given the tablets' small size. Note that the tablet weight for the 8mg is twice that of the 4mg indicating a dose proportional formulation is likely used. This approach was used for the development of the prototype formulations with **PROSOLV® ODT G2**.

Materials

PROSOLV® ODT G2 is a high functionality excipient for orally disintegrating tablet formulation, development and manufacture. It provides functional performance needed for today's orally disintegrating tablet formulations. It is comprised of microcrystalline cellulose, colloidal silicon dioxide, mannitol, fructose and crospovidone. Ondansetron USP was supplied as a white powder with poor flow. A strawberry flavor was also included to improve the taste.

Formulation Studies

Prototype Development

The prototype formulations were developed to be simple from both a component and process standpoint. The main component in the formulation is **PROSOLV® ODT G2**, which imparts the characteristics necessary to manufacture an ODT formulation. Also, using **PROSOLV® ODT G2** it was possible to reduce the number of ingredients from nine to four. The API was blended directly with the excipient along with strawberry flavor. Screened **PRUV®** Sodium Stearyl Fumarate (SSF) was then blended in the formulation for the purpose of tablet lubrication.

The formulation for trials 1 and 2 is shown in Table 2.

Component	%	mg/tab	mg/tab
Ondansetron	7.1	5.0	10.0
PROSOLV® ODT G2	90.9	63.6	127.2
Strawberry Flavor	1	0.7	1.4
PRUV® SSF	1	0.7	1.4
Total	100	70	140

Tab. 2 Trial 1 and 2 Tablet Formulations

Processing steps:

1. Screen Ondansetron through a 20 mesh screen
2. Blend Ondansetron, flavor and **PROSOLV® ODT G2** for 5 minutes in a Turbula mixer
3. Screen **PRUV®** through a 20 mesh screen
4. Blend with **PRUV®** for 5 minutes in a Turbula mixer
5. Compress into tablets and obtain compaction profile
6. Tooling sizes are 0.25” and 0.28” for the 5 mg and 10 mg respectively.

Tablets were compressed at different hardness to assess the impact of compression force on tablet disintegration.
Tablets were tested for disintegration in water and the results are displayed in Figure 1.

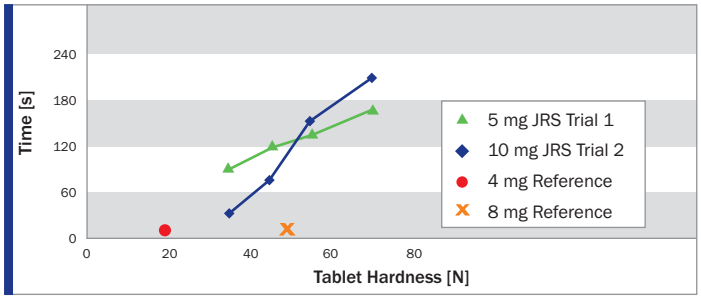

Fig. 1 Disintegration Times for the Prototype Formulation

Figure 1 shows the impact that tablet hardness has on disintegration time. As the tablet hardness increases, so does the time for disintegration. When compared to the reference product, the prototype trial tablets took longer to disintegrate.
Note that this is seen for both strengths. The disintegration times for the reference product are less than 20 seconds and are also included in Figure 1.

Optimization Step

Based on the longer disintegration times obtained from the prototype formulation, additional disintegrant (**VIVAPHARM® PVPP XL10**) was added. The crospovidone was blended with the **PROSOLV® ODT G2**, API, and flavor, prior to blending with the tablet lubricant (**PRUV®**).

The formulation for trials 3 and 4 is listed in Table 3.

Component	%	mg/tab	mg/tab
Ondansetron	5.7	4	8
PROSOLV® ODT G2	90.3	63.2	126.4
Crospovidone XL10	2	1.4	2.8
Strawberry Flavor	1	0.7	1.4
PRUV® (Sodium Stearyl Fumarate)	1	0.7	1.4
Total	100	70	140

Tab. 3 Optimization Trial

Disintegration results for the optimized formulations are shown in Figure 2.

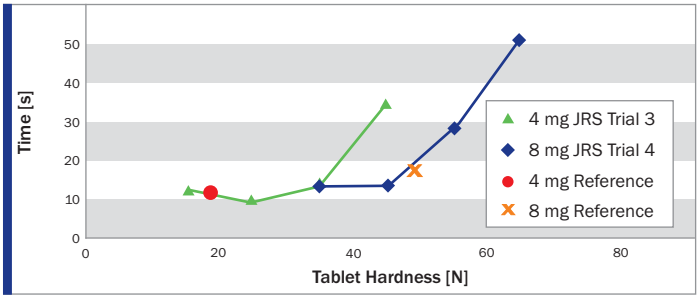

Fig. 2 Disintegration Times for the Optimized Formulations

The tablets disintegrated much faster after optimization when compared to the prototype formulation, which is due to the inclusion of additional disintegrant. The effect of tablet hardness on disintegration time is similar to what was observed in step 1. More notable is that the disintegration times achieved are similar to the reference products at tablet hardness of ~20 and ~40N respectively. Tablet friability testing at these hardness levels was acceptable.

Conclusion

The prototype formulation containing **PROSOLV® ODT G2**, drug and flavors produced quickly disintegrating tablets with fewer ingredients than the marketed product.
Adding additional Crospovidone (PVPP XL10) to the formulation (Optimization Step) dramatically reduced the time for tablet disintegration and was comparable to the marketed product. Tablets were made via direct compression process using standard processing equipment. The flavor level in the formula would likely need to be adjusted to achieve acceptable palatability of the final product.

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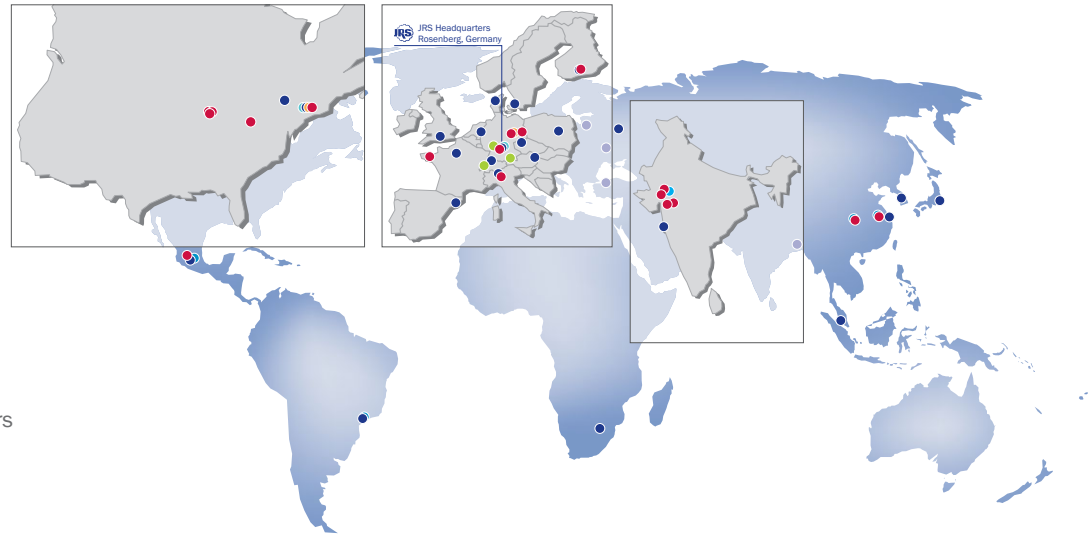

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PROSOLV® SMCC
Silicified Microcrystalline Cellulose

PROSOLV® EASYtab SP
Microcrystalline Cellulose, Colloidal Silicon Dioxide, Sodium Starch Glycolate, Sodium Stearyl Fumarate

PROSOLV® EASYtab NUTRA
All-in-one Composite for Nutraceutical Applications

PROSOLV® ODT G2
Microcrystalline Cellulose, Colloidal Silicon Dioxide, Mannitol, Fructose, Crospovidone

DISINTEGRANTS

VIVASTAR®, EXPLOTAB®
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VIVASOL®
Croscarmellose Sodium

EMCOSOY®
Soy Polysaccharides

VIVAPHARM® Crospovidone
Polyvinylpyrrolidone, crosslinked

COATINGS

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Ready-to-Use High Functional Coating System

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Hypromellose

VIVAPHARM® PVA
Polyvinyl Alcohol

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EMDEX®
Dextrates

VIVAPHARM® Povidones
Povidone and Copovidone

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LUBRITAB®
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LUBRI-PREZ™
Magnesium Stearate

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Sugar Pellets, Non-GMO

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EMCOMPRESS®
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COMPACTROL®
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THICKENERS • STABILIZERS • GELLING AGENTS

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VIVAPHARM® Alginates
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