Directly Compressed Orally Disintegrating Tablets for Paediatric Drug Delivery: A Novel Heat-Cool Process Strategy

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Sep 2012
Outline

Oral Paediatric Formulations

What’s an ODT?

Why ODTs?

Methods of Manufacture

Direct Compression

Heat-Cool Process

Characterization

Effect of Hot Blending

Advantages and Challenges

Summary
Oral Paediatric Formulations

- Oral liquid formulations (solutions and suspensions)
- Powders for constitution in suspension or solution or for sprinkle over food/drink
- Solid dosage forms such as ODTs, chewable and effervescent tablets
What’s an ODT?

US FDA defined orally disintegrating tablet as “A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.”

- Orodispersible, Fast melts, Fast dissolving, Rapidly disintegrating...
- FDA Guidance specifies 30 seconds for disintegration time
- Eur Pharmacopeia specifies < 3 minutes for disintegration time
Why ODTs?

- **Swallowing process:** may be difficult for children below 6 years of age
- **Safety:** risk of choking or aspiration
- **Stability:** microbial, physical, chemical degradation
- **Dose uniformity and accuracy:** low dose drugs
- **Patient Compliance:** adherence to medication e.g. > 92% of children aged 6-11 yrs. (n=104) preferred strawberry flavoured lansoprazole ODT over peppermint-flavoured formulation
Why ODTs?

- **Pharmacokinetic advantage**: rapid onset of action due to buccal or pregastric absorption or reduction in disintegration time
  - *e.g.* Similar control of emesis was found between ondansetron ODT and IV formulation in children undergoing cancer chemotherapy.

- **Practicality**: cost-effective, handling and transport
  - *e.g.* ODT of Ondansetron was cheaper than IV formulation
Methods of Manufacture

Freeze Dried ODTs

Shearform Matrix ODTs

Directly Compressed ODTs
Direct Compression of ODTs

- Low manufacturing cost allows development of more products adapted for different age and dosing requirements
- Accommodate high dose drugs in contrast to freeze dried ODTs (< 20 mg)
- No specialized packaging is needed as the tablets are mechanically strong
Heat/Cool Process: The principle

Mannitol + TPGS
Cold (25°C) or Hot Blending (40°C)
followed by Compression

Disintegration at body temperature

TPGS melts at 37°C
• Inclusion of TPGS reduced disintegration time to 60 sec as a result of melting at 37°C
## ODT Characterization

<table>
<thead>
<tr>
<th>Process</th>
<th>Particle size of mannitol (µm)</th>
<th>Hardness (N)</th>
<th>Disintegration time (sec)</th>
<th>Friability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold Process</td>
<td>63</td>
<td>36.7±2.31</td>
<td>95.7±4.62</td>
<td>3.16</td>
</tr>
<tr>
<td></td>
<td>&lt; 53</td>
<td>35.3±1.53</td>
<td>74.7±0.58</td>
<td>2.73</td>
</tr>
<tr>
<td>Hot Process</td>
<td>63</td>
<td>38.7±4.73</td>
<td>72±7.81</td>
<td>1.77</td>
</tr>
<tr>
<td></td>
<td>&lt; 53</td>
<td>29.3±2.08</td>
<td><strong>461±7.93</strong></td>
<td>1.74</td>
</tr>
</tbody>
</table>
D-Mannitol Morphology

- Longitudinal/needle shaped particles with rough/irregular surfaces

- Needle shaped particles are considered loosely packed systems

- Fragmentation occurred possibly due to breakage of the rough surfaces
• Fragmentation of D-mannitol resulted in poor compacts which was attributed to high die-wall pressure during compaction
Effect of Hot Blending

- Heating at 40°C melted TPGS which enhanced its distribution between the diluent (D-mannitol) particles

- This enhanced inter-particulate bonding potentially by solid bridges between adjacent D-mannitol particles leading to lower tablet friability
## Advantages and Challenges

<table>
<thead>
<tr>
<th>Process-related</th>
<th>Advantages</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• <strong>Cost-effective</strong> due to the use of conventional tableting machine</td>
<td>• Segregation, <strong>flowability</strong>, dusting</td>
</tr>
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<td></td>
<td>• <strong>Good Mechanical Strength</strong>, resist fracturing during handling and opening of blister pockets</td>
<td></td>
</tr>
<tr>
<td>Excipient-related</td>
<td>• ‘<strong>Sugar Free</strong>’ formulation due to inclusion of mannitol (polyol) which does not cause dental caries</td>
<td>• <strong>Friability</strong> due to D-mannitol</td>
</tr>
<tr>
<td></td>
<td>• TPGS forms micelles in solution thus it is useful for solubilisation of <strong>poorly soluble drugs</strong></td>
<td></td>
</tr>
</tbody>
</table>
Summary

- ODTs potentially improve health outcomes in paediatric populations
- ODTs available commercially are mostly prescribed for pediatrics 6-18 years of age
- Direct compression may provide a cost-effective alternative for the production of ODTs
- D-mannitol is an important excipient in the development of ODTs, yet, it undergoes fragmentation under pressure causing high friability
- Addition of TPGS not only reduced disintegration time, but also helped producing less friable tablets when heated
Acknowledgements

**Supervisor:**
Dr Afzal R Mohammed

**Associate Supervisors:**
Prof. Yvonne Perrie
Dr Peter Rue

Technical Staff and Colleagues at the Drug Delivery Research Group (DDRG)

Our Research Group

Aston University
Birmingham

BBSRC
EPSRC
MRC
Aston University
Colorcon
Viridian Pharma Ltd
Wellcome Trust
Advantage West Midlands
Pharma Spec Specials
Apex Healthcare Ltd
Any Questions?