Dosage Form Design for the Elderly

Prof. Dr. Pornsak Sriamornsak

Faculty of Pharmacy, Silpakorn University
Pharmaceutical Biopolymer Group, Silpakorn University
Academy of Science, The Royal Society of Thailand
Thai Industrial Pharmacist Association
The median age of continents

Africa has the world’s youngest population, with a median age in the teens.

**The Median Age of Continents**

- **Canada**: 42.2
- **U.S.A.**: 38.1
- **Mexico**: 28.3
- **Monaco**: 53.1
- **Afghanistan**: 18.8
- **Japan**: 47.3

In North America, major economies have different age profiles.

Belize and Guatemala are the youngest countries in the Americas.

By 2100, close to half of the world’s kids (age 0-4) will live in Africa.

- **2020**: 173M
- **2050**: 506M
- **2100**: 293M
- **2100**: 377M

Sub-Saharan Africa Rest of World
Main reasons for elderly population growth
1. The success in public health policy and medical advancement cause of reduction in death rate
2. Economic development and national development
Problems and challenges for medicine in elderly

10 Common Chronic Condition for Elderly

- Hypertension (High Blood Pressure): 58%
- High Cholesterol: 47%
- Arthritis: 31%
- Ischemic Heart Disease (or Coronary Heart Disease): 29%
- Diabetes: 27%
- Chronic Kidney Disease: 18%
- Heart Failure: 14%
- Depression: 14%
- Alzheimer’s Disease and Dementia: 11%
- Chronic Obstructive Pulmonary Disease: 11%

80% Have at least 1 chronic condition
68% Have 2 or more chronic conditions

Source: Centers for Medicare & Medicaid Services, Chronic conditions Prevalence Stage/County table: All-for-Service Beneficiaries. 2015
Problems and challenges for medicine in elderly

Physiological changes on aging

### Decreasing of Efficacy and Safety

#### Absorption and distribution in the older adults

<table>
<thead>
<tr>
<th>Factors impacting absorption</th>
<th>Factors impacting distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of saliva ↓</td>
<td>Cardiac output ↓</td>
</tr>
<tr>
<td>Gastric acid production ↓</td>
<td>Renal blood flow ↓</td>
</tr>
<tr>
<td>Gastro-intestinal surface ↓</td>
<td>Hepatic blood flow ↓</td>
</tr>
<tr>
<td>Active transport mechanism ↓</td>
<td>Albumin water levels ↓</td>
</tr>
<tr>
<td>Gastric pH ↑</td>
<td>Volume of distribution for water soluble drugs ↓</td>
</tr>
<tr>
<td>Gastric emptying time ↑</td>
<td>Peripheral vascular resistance ↑</td>
</tr>
<tr>
<td></td>
<td>Body fat/water ratio ↑</td>
</tr>
<tr>
<td></td>
<td>Volume of distribution for lipid soluble drugs ↑</td>
</tr>
</tbody>
</table>

#### Metabolism and elimination in the older adults

<table>
<thead>
<tr>
<th>Factors reducing metabolism</th>
<th>Factors reducing elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver function (through decrease in blood flow and hepatic mass) ↓</td>
<td>Kidney size ↓</td>
</tr>
<tr>
<td>Cyp P450 enzyme levels ↓</td>
<td>Renal blood flow ↓</td>
</tr>
<tr>
<td>Overall drug metabolism ↓</td>
<td>Number of functional nephrons ↓</td>
</tr>
<tr>
<td></td>
<td>Tubular secretion ↓</td>
</tr>
</tbody>
</table>

↓, the factor is reduced.


Effect of Aging on Body Physiology

Polypharmacy

The concurrent use of multiple medications by a patient

Compliance Adherence Efficacy Safety
Problems and challenges for medicine in elderly

Polypharmacy

**Decreasing of Compliance, Adherence and Safety**

- Polypharmacy, the use of more than 5 different drugs simultaneously, is very common in older adults.

- Most elderly patients have poor memories and get confused.

- They may live alone, or with a partner who is no better. They find it difficult to follow even simple instructions, and the complicated schedules sometimes offered, with many drugs to be taken at different times.
The selection and design of patient-centered oral pharmaceutical dosage forms continues to be one of the most significant challenges in the development of medicinal products for elderly populations due to the diverse needs and characteristics of these patient groups.
Problems and challenges in oral drug delivery technologies

- While the oral route is the most convenient method of drug administration, advances in oral drug delivery technologies have been limited.
- One of the reasons for this is the limitations imposed by the unique GI physiology.
- Even small improvements in drug delivery technology can make significant differences in enhancing patient compliance and drug bioavailability.

(A) Mouth; (B) Stomach; (C) Small intestine; (D) Colon
Swallowing considerations *(Oral delivery)*

- It is estimated that approximately one-third of the population has *pill-swallowing difficulties*, primarily the elderly populations.

- Modification of the dosage form in terms of capsule opening and tablet crushing is considered as a common practice in nursing homes. This has the following consequences:
  - Uncoated or large tablets can be difficult to swallow.
  - Older adults may often resort to crushing, chewing or splitting tablets with the risk of not receiving the full dose.
  - The contents of a capsule or a crushed tablet may be mixed with food to facilitate swallowing and this may lead to poor or inappropriate dosing or compatibility issues.
The factors to consider for elderly oral dosage form design in relation to these 3 criteria

1. Acceptable tolerability and safety
2. Dosage preparation
3. Ease of ingestion

Patient Acceptability

1

Safety

2

Access

3

Dosage consideration
Risk of mis-dosing

Stability

Manufacturing and development complexity
Supply chain
Relative cost
Orally Disintegrating Tablet (ODT) is a solid dosage form containing drugs that disintegrates rapidly and dissolves in the mouth without taking water within 60 seconds or less.
**Oral disintegrating tablets (ODT)**

Orally Disintegrating Tablet (ODT) is also called as *oro-disperse*, *mouth dissolving*, *rapidly disintegrating*, *fast melt*, *quick dissolve* and *freeze dried wafers*.
Formulations for ease of administration (ODT)

Some ODTs in the market and name of patented ODTs technologies, their basis and advantages

<table>
<thead>
<tr>
<th>Active Ingredients</th>
<th>Category</th>
<th>Manufacturing Technology</th>
<th>Technological basis</th>
<th>Advantages of technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loratadine</td>
<td>Antihistaminic</td>
<td>Zydis*</td>
<td>Lyophilization</td>
<td>Very fast disintegration (2-10 sn)</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Antidepressant</td>
<td>Orasolv*</td>
<td>Compressed tablets</td>
<td>Effervescent disintegration</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Antipsychotic; Serotonin-Dopamine Antagonist</td>
<td>Zydis*</td>
<td>Lyophilization</td>
<td>Very fast disintegration (2-10 sn)</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Nootropic; Antiemetic; Serotonin Receptor Antagonist</td>
<td>Zydis*</td>
<td>Lyophilization</td>
<td>Very fast disintegration (2-10 sn)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Antipsychotic; Dopamine Receptor Antagonist; Serotonin-Dopamine Antagonist</td>
<td>Zydis*</td>
<td>Lyophilization</td>
<td>Very fast disintegration (2-10 sn)</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>Antimigraine; Serotonin Receptor Agonist</td>
<td>Zydis*</td>
<td>Lyophilization</td>
<td>Very fast disintegration (2-10 sn)</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Analgesic (Non-narcotic)</td>
<td>FlashDose*</td>
<td>Cotton Candy Process</td>
<td>Effectively taste maske</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Antimigraine; Serotonin Receptor Agonist</td>
<td>DuraSolv*</td>
<td>Compressed tablets</td>
<td>Easy to formulate low dose of active ingredient and higher mechanical strength than Orasolv</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Sedative/Hypnotic</td>
<td>FlashDose*</td>
<td>Cotton Candy Process</td>
<td>Effectively taste maske</td>
</tr>
</tbody>
</table>

## Formulations for ease of administration (ODT)

**Advantages of ODTs**

- Administration to the patients who cannot swallow, such as the elderly, stroke victims, patients who refuse to swallow
- Rapid drug therapy intervention
- Achieve increased bioavailability/rapid absorption through pre-gastric absorption of drugs
- Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water

**Disadvantages of ODTs**

- Hygroscopic in nature
- Low amount of drug can be incorporated in each dose
- Some time it possesses mouth feeling
- Highly fragile sometimes
- ODT requires special packaging for properly stabilization & safety of stable product
- Eating and drinking may become restricted
Formulation Development of ODTs

Active pharmaceutical ingredient

- It should be dissolved in the oral cavity and absorbed
- It shouldn’t have bitter taste
- It is in low dose, small to moderate molecular weight, good solubility in water and/or saliva
- Non-ionized property in pH 5.5-7.4

Excipient selection

- It is important for disintegrating the tablet immediately and also important for masking bitter taste
- Main excipient groups are
  - Diluents
  - Disintegrants
  - Flavors and taste masking agents
  - Sweeteners
  - Binders
  - Lyoprotectants
  - Glidants and lubricants
Formulations for ease of administration (ODT)

- WOWTAB®
- ORASOLV®
- DURASOLV®
- ADVATAB®
- FLASHTAB®

Conventional tablet process with modification

Freeze drying method

- ZYDIS®
- LYOC®
- QUICKSOLV®

Floss formation
(Cotton Candy Process)

- FLASHDOSE®
## Formulations for ease of administration (ODT)

<table>
<thead>
<tr>
<th>Technology</th>
<th>In vitro disintegration time (s)</th>
<th>Tablet hardness and robustness</th>
<th>Packaging</th>
<th>Drug-loading dose (mg)</th>
<th>Marketed products worldwide</th>
</tr>
</thead>
<tbody>
<tr>
<td>AdvaTab (Eurand)</td>
<td>15–30</td>
<td>hard, robust</td>
<td>bottles or blister pack</td>
<td>&lt;700</td>
<td>2</td>
</tr>
<tr>
<td>DuraSolv (CIMA Labs)</td>
<td>&lt;30</td>
<td>hard, robust</td>
<td>bottles or blister pack</td>
<td>&lt;500</td>
<td>3</td>
</tr>
<tr>
<td>FlashDose (Biovail)</td>
<td>5–15</td>
<td>soft, friable</td>
<td>blister pack</td>
<td>&lt;600</td>
<td>1</td>
</tr>
<tr>
<td>FlashTab (Ethypharm SA)</td>
<td>30–60</td>
<td>relatively durable</td>
<td>blister pack</td>
<td>&lt;650</td>
<td>3</td>
</tr>
<tr>
<td>Lyoc (Cephalon)</td>
<td>&lt;10</td>
<td>soft, friable</td>
<td>blister pack</td>
<td>&lt;1000</td>
<td>6</td>
</tr>
<tr>
<td>OraQuick (KV Pharmaceuticals)</td>
<td>&lt;20</td>
<td>relatively durable</td>
<td>bottles or blister pack</td>
<td>&lt;500</td>
<td>1</td>
</tr>
<tr>
<td>OraSolv (CIMA Labs)</td>
<td>&lt;30</td>
<td>soft, fragile</td>
<td>blister pack</td>
<td>&lt;750</td>
<td>3</td>
</tr>
<tr>
<td>SATAB (Sato)</td>
<td>&lt;10</td>
<td>relatively durable</td>
<td>blister pack</td>
<td>&lt;600</td>
<td>7</td>
</tr>
<tr>
<td>WOWTAB (Yamanouchi)</td>
<td>&lt;30</td>
<td>relatively durable</td>
<td>bottles or blister pack</td>
<td>&lt;500</td>
<td>14</td>
</tr>
<tr>
<td>Zydis (Cardinal Health)</td>
<td>3–5</td>
<td>very fragile</td>
<td>blister pack</td>
<td>&lt;400</td>
<td>15</td>
</tr>
</tbody>
</table>

Source: http://pharmtech.findpharma.com/pharmtech/article/articleDetail.jsp?id=185957
Formulations for ease of administration (ODT)

- WOWTAB®
- ORASOLV®
- DURASOLV®
- ADVATAB®
- FLASHTAB®

Conventional tablet process with modification

Freeze drying method

- ZYDIS®
- LYOC®
- QUICKSOLV®

Floss formation
(Cotton Candy Process)

- FLASHDOSE®

ZipDose® Technology
(3D printing technique)
Formulations for ease of administration (ODT)

- In 2015, FDA Approves as the First 3D Printed Drug Product by Aprecia Pharmaceuticals
- Pill can be made more porous than typical pills, rapidly disintegrate
- Support dose loading up to 1,000 mg

First, a powdered medicine is spread into a thin layer

Then, a liquid is dropped onto the powder

This selectively binds the particles together in a thin, porous layer

This process is repeated a specific number of times to add more layers based on the dosage, building the product from bottom to top
Challenges in ODTs

- Disintegration time and mechanical strength
- Taste masking
- Sensitivity to environmental conditions
- Mouth feel
- Cost

Formulations for ease of administration (ODT)
Other dosage forms and innovations

Swallowing Aid Jelly

A jelly to swallow medicine easily and tastily.

For children!
When children reject to take medicine, there is a possible choking or difficulty in swallowing.

Adults (Dislike to take medicine)
Difficult to swallow multiple medicines at once. Not good at taking powder medicines spreading inside the mouth. Uncomfortable taking medicines and supplements.

Elderly people
(Having difficulty with swallowing)
Due to aging, swallowing muscle starts to feel pain becoming difficult to swallow.

People having difficulty to swallow
Swallowing and pharynx muscles getting weak diagnosed with vascular disorders (potential pseudobulbar paralysis etc.), carrying difficulties to swallow.

Before use
- After you open, throw away the liquid on the top layer. There will be no effect drinking this liquid.

Step 1 Using a cup
- Pour jelly in the cup.
- Put all tablets and capsules together into the cup. Cover them up with jelly.
- Do the same as above for powdered medicine.
- It’s like wrapping up the medicine with jelly.

Step 2 Using a spoon
- Pour the certain amount of jelly on the spoon.
- Put medicine on top of it and pour more jelly to cover it.

Step 3 Substitution of water
- Take medicine using Swallowing Aid Jelly (Magic Jelly) instead of water.
Other dosage forms and innovations

Swallowing Aid Jelly

• Stress on the throat, when swallowing

The above shows that the throat experiences stress when medicines are taken with “water”.

When medicines are taken with “jelly”, the throat does not experience any stress.

• Time to reach the stomach.

“Water” takes as much as approx. 18 seconds to reach the stomach.

“Jelly” takes only approx. 8 seconds to reach the stomach.

Source: https://www.ryukakusan.co.jp/company/en#company_03
Other dosage forms and innovations

Swallowing Flavored Spray

A flavored spray product requires the patient to apply the spray to the back of the mouth and tongue before taking tablets or capsules. The spray creates a lubricated surface in the mouth and thus facilitates swallowing. It has been found to be helpful in adolescents with difficulties in swallowing tablets.

**Spray Pill Glide in mouth** (2-4 sprays is sufficient for most people to coat their tongue and throat).

**STEP 1**

**STEP 2**

**STEP 3**

Place tablet or capsule in your mouth.

Swallow with a few sips of water.
Pill Coating

• **Easier to swallow:**
  The coating is slippery and saliva stimulating which make tablets easier to swallow.

• **Taste good:**
  The coating masks the taste of tablets and replaces it with a pleasant and refreshing taste of citrus.
Other dosage forms and innovations

Pill Coating

1. Peel off the foil from both the top and bottom side.

2. Push the tablet through the opening (yellow area) on the top side. See figure 6 for round or divided tablets.

3. Keep pushing until the whole tablet is coated. Thereafter wait for five seconds.

4. Twist the tablet two turns without pulling.

5. Remove the tablet by pulling it quickly. Swallow the coated tablet with water.

6. The figure above shows how to push through different types of whole and divided tablets.
A polypill is a medication that is a drug product in pill form (i.e., tablet or capsule) that combines multiple active pharmaceutical ingredients.

It is commonly manufactured as a fixed-dose combination (FDC) drug product targeting treatment or prevention of chronic disease.

Polypills can reduce the number of tablets or capsules (generally orally administered) that need to be taken, which in turn may facilitate handling and administration of pharmaceuticals as well as alleviate patient pill burden.
### Other dosage forms and innovations

#### Polypill Technology

A list of selected examples of commercially available FDCs in these therapeutic areas

<table>
<thead>
<tr>
<th>Diabetes</th>
<th>HIV/AIDS</th>
<th>Cardiovascular diseases</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actoplus Met (pioglitazone/metformin: 15/500 mg, 15/850 mg)</td>
<td>Atripla (efavirenz/emtricitabine/tenofovir: 600/200/300 mg)</td>
<td>Simcor (niacin ext/simvastatin: 500/20 mg, 750/20 mg, 1000/20 mg)</td>
<td>Treximet (sumatriptan/naproxen: 85/500 mg)</td>
</tr>
<tr>
<td>Avandamet (rosiglitazone/metformin: 2/500 mg, 4/500 mg, 2/1000 mg)</td>
<td>Combivir (lamivudine/zidovudine: 150/300 mg)</td>
<td>Advicor (niacin/lovastatin: 500/20 mg, 750/20 mg, 1000/20 mg, 1000/40 mg)</td>
<td>Tylenol with codeine (paracetamol/codeine: 300/30 mg, 300/60 mg)</td>
</tr>
<tr>
<td>Avandary (rosiglitazone/glimepiride: 4/1 mg, 4/2 mg, 4/4 mg, 8/2 mg, 8/4 mg)</td>
<td>Eqzicom (abacavir/lamivudine: 600/300 mg)</td>
<td>Kaletra (lopinavir/ritonavir: 200/50 mg, 100/25 mg)</td>
<td></td>
</tr>
<tr>
<td>Duetact (pioglitazone/glimepiride: 30/2 mg, 30/4 mg)</td>
<td>Kaletra (lopinavir/ritonavir: 200/50 mg, 100/25 mg)</td>
<td>Caduet (amlodipine/atorvastatin: 2.5/10 mg, 2.5/40 mg, 5/10 mg, 10/40 mg, 10/80 mg)</td>
<td></td>
</tr>
<tr>
<td>Glucovance (glyburide/metformin: 12.5/250 mg, 2.5/500 mg, 5/500 mg)</td>
<td>Trizivir (abacavir/lamivudine,zidovudine: 300/150/300 mg)</td>
<td>Accuretic (quinapril/HCTZ: 10/12.5 mg, 20/12.5 mg, 20/25 mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diovan HCT (valsartan, HCTZ:80/12.5 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg, 320/25 mg)</td>
<td></td>
</tr>
</tbody>
</table>

**Source:** [https://www.americanpharmaceuticalreview.com/Featured-Articles/117118-Manufacturing-Process-Considerations-for-Fixed-Dose-Combination-Drug-Products/](https://www.americanpharmaceuticalreview.com/Featured-Articles/117118-Manufacturing-Process-Considerations-for-Fixed-Dose-Combination-Drug-Products/)
Disadvantages of the FDC products

1. FDC products reduce dosing flexibility.

2. The adverse drug reactions of the FDC products as more than one drug is administered in a single dosing unit.

3. Pharmacists and physicians can easily overlook the limit of certain drugs in FDCs, because some patients cannot use drug dosing that contained in a tablet for their treatment.

4. The FDC contains multiple drugs in one tablet, sometimes, the tablet size may be too big to swallow for elderly patients.
Polypill Technology

Formulation development challenges and strategies for FDC oral solid dosage forms

- Physicochemical compatibility among all drugs as well as excipients in FDCs
- Disproportionate drug dose combinations can be very challenging in achieving good content uniformity, especially in weight control of low dose layer of multilayer tablets that contains low dose in the second layer
- The tablet size of the FDC product can become critical in achieving patient acceptance
Legal and professional implications

- Off-label drug use (opening a capsule or crushing a tablet before administration)
- Lack of consent for administration (patient may be unaware of medication provided in food)
- Cross contamination (one crushing device being used for multiple patients’ medicines, placing patients at risk of adverse effects such as allergic reactions)
Conclusions

Age-related changes in physiological functionality of tissues and organs

Pharmacokinetic changes

Chronic diseases

Polypharmacy

Compliance

Adherence

Efficacy

Safety

The factors to consider for elderly dosage forms design and development

Acceptability

1. Acceptable tolerability and safety
2. Dosage preparation
3. Ease of ingestion

Safety

1. Dosage consideration
2. Risk of mis-dosing

Access

1. Stability
2. Manufacturing and Development complexity
3. Supply chain
4. Relative cost

Oral dosage forms

Swallowing difficulty

Polypharmacy

ODTs, swallowing devices

Polypill technology

Compliance

Adherence

Efficacy

Safety
Thank you

Thanks also go to K. Thanawuth for graphic design and slide preparation