Formulation of Incrementally Modified Drugs by Combination

Pharmaceutical Research Center

Yong-il Kim

Hanmi Pharm. Co., Ltd.
Hanmi Pharmaceutical

- **Founder**: Sung-Ki, Lim
- **Foundation**: June 15, 1973
- **Total employees**: 1,950 (442 R&D, 2015)
- **Total Sales**: USD 761 mil (2014)

Chairman Sung-Ki Lim
Part 1. Hanmi’s FDC Development Work

Part 2. Practical FDC products by platforms

- Monolithic tablet: Amosartan®
- Bi-layer tablet: Rovelito®
- PolyCap: Monterizin®, Dutams®

Part 3. Summary & conclusion
Part 1. Hanmi’s FDC Development Work
1. **Better efficacy: Synergistic mechanism, Improved ADME**
   - Drugs with different treatment mechanism (Amlodipine + Valsartan: Exforge)
   - Immediately acting drug + long acting drug (Salmeterol + Fluticasone: Advair)
   - Drug + Adverse effect-reducing drug (Naproxen + Esomeprazole: Vimovo)

2. **Less adverse event: than a higher dose of single drug**
   - Low dose of 2 drug-combination is more effective than higher dose of single drug
     (Statin + Ezetimibe: Vytorin, Atozet)

3. **Improved patient compliance: Simplified medication**
   - Two or three drugs in one pill (Exforge HCT: 3 drugs in 1 pill)
   - Harmonized dosing regimen (Vimovo)

➤ Many of treatment guidelines recommended combined administration (FDC)
   (JNC8-hypertension, GOLD-COPD, ADA Diabetes Care – Diabetes)
4. Economic benefits
   - Lower manufacturing cost
   - Lower medication cost

5. Extended ‘Drug Life Cycle’
   - extended duration of exclusive rights by combination (data exclusivity, patent)
     - Exforge, Vimovo, Jalyn, Vytorin…

6. Faster commercialization
   - Abbreviated clinical study & Low RA huddle than NCE
Many global companies have been working on FDC products and received approval from the FDA, since 1990’s

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adderall</td>
<td>Shire</td>
<td>1996</td>
</tr>
<tr>
<td>Suboxone</td>
<td>Reckitt-Benckiser</td>
<td>2002</td>
</tr>
<tr>
<td>Avalide</td>
<td>Sanofi</td>
<td>1997</td>
</tr>
<tr>
<td>Diovan HCT</td>
<td>Novartis</td>
<td>1998</td>
</tr>
<tr>
<td>Exforge</td>
<td>Novartis</td>
<td>2007</td>
</tr>
<tr>
<td>Lotrel</td>
<td>Novartis</td>
<td>1995</td>
</tr>
<tr>
<td>Micardis HCT</td>
<td>Boehringer-Ingelheim</td>
<td>2000</td>
</tr>
<tr>
<td>Vytorn</td>
<td>Merck</td>
<td>2004</td>
</tr>
<tr>
<td>Janumet</td>
<td>Merck</td>
<td>2007</td>
</tr>
<tr>
<td>Yasmin</td>
<td>Bayer</td>
<td>2001</td>
</tr>
<tr>
<td>Atripla</td>
<td>Gilead</td>
<td>2006</td>
</tr>
<tr>
<td>Combivir</td>
<td>GlaxoSmithKline</td>
<td>1997</td>
</tr>
<tr>
<td>Epzicom</td>
<td>GloxoSmithKlin</td>
<td>2004</td>
</tr>
<tr>
<td>Truvada</td>
<td>Gilead</td>
<td>2004</td>
</tr>
<tr>
<td>Advair</td>
<td>GlaxoSmithKline</td>
<td>2000</td>
</tr>
<tr>
<td>Combivent</td>
<td>Boehringer-Ingelheim</td>
<td>1996</td>
</tr>
<tr>
<td>Symbicort</td>
<td>AstraZeneca</td>
<td>2006</td>
</tr>
<tr>
<td>Complera</td>
<td>Gilead</td>
<td>2011</td>
</tr>
</tbody>
</table>
Combination rationale

- Clinical evidence (synergic effect, reducing adverse effects)
- Co-prescription frequency/ratio in the field

Drug-Drug interaction

- Absorption mechanism of each drug
- Metabolism pathway of each drug
  - Low possibility of interaction is ideal (Safety / RA perspective)

Dosing regimen

- Same dosing regimen is preferred
- If not same; Harmonized / clinically proved dosing regimen is necessary
  (need to conduct clinical study)
• Consideration of physiochemical properties of each drug

  ▪ Polymorphism
  ▪ Solubility
  ▪ Stability (in the stress condition)
  ▪ Degradation pathway
  ▪ Compatibility with excipients
  ▪ Target effective dose
  ▪ Target release profile
  ▪ etc

 ➔ Considering these properties formulation study is performed
Challenges of a FDC formulation

- Should consider Inter-API interaction
  - Chemical interaction (ex. acid/base reaction)
  - Physical interaction (effect on the drug release)

- Should make an one-dosage form which is bioequivalent to each RLD
  - Formulate to have a comparable release profile of each RLD
  - If not, additional clinical studies are required (dose finding, safety, efficacy, …)

- Should consider a product size
  - FDC tends to be bigger than a single product
  - Smaller size is preferred

Considering challenges above, we need to study to find out a suitable FDC dosage form
Platforms of FDC dosage form in Hanmi 1/2

- Conventional monolithic tablet
- Bi-layer tablet

**Multi-layer Coated Tablet / Capsule & its expansion**

One API is in a core + other API is in a coated layer

- Plain tablet (IR or SR) / Coated layer (IR)
- Bi-layered Tablet (IR or SR) / Coated layer (IR)
- Multi-unit Tablet (IR & SR) / Coated layer (IR)
- Hard capsule (Polycap) / Coated layer (IR)
- Soft capsule / Coated layer (IR)

By changing the core, various different expansions are possible.
PolyCap

*Innovative technology for FDC*

Capsule, filled with 2~3 different dosage forms

[ pellet x granule x tablet x mini tablet x soft/hard capsule]

- Easy to make a combination drug
- Retain each dosage forms
- Retain each drug release characteristic
- Improved stability (no drug-drug interaction)

Most ideal formulation concept for FDC

In hanmi
3 stations for conventional tablet
1 station for 10 mini tablets
1 station for 20 mini tablets
1 station for pellet
1 station for granule(powder)
Part 2. Practical FDC products by platforms

- Monolithic tablet: Amosartan®
- Bi-layer tablet: Rovelito®
- PolyCap: Dutams®, Monterizin®
2-1. Monolithic tablet

- Amosartan® tablet
One of the most ideal combination drugs for a treatment of high blood pressure

- **Losartan potassium**
  - Angiotensin Receptor Blocker

- **Amlodipine camsylate**
  - Calcium Channel Blocker

- **Norvasc**
  - (amlodipine 5,10mg, besylate)

- **Cozzar**
  - (losartan K 50,100mg)

- Amlodipine camsy. + Losartan K
  - 3 different dose strengths
    - 5/50, 5/100, 10/50
Formulation challenges

- **Alternative salt of amlodipine**
  - patent issue
  - poor solubility

  ➔ Need to improve solubility of amlodipine camsylate salt

- **Inter-API interaction**
  ➔ Losartan influence on the dissolution & degradation of Amlodipine

  ➔ Need to overcome inter-API Interaction

Losartan ➔ Amlodipine
For improving solubility of Amlodipine camsylate:

Spray drying to change the crystalline form into an amorphous form.

Solubility test of Amlodipine camsylate (Basket, 100rpm, Water):

- Amorphous form: Increased solubility (2 times) by spray drying.
- Crystalline form:

XRD of Amlodipine camsylate:

- Amorphous form
- Crystalline form
Utilized two different types of disintegration agent (cros-carmellose Na / cros-povidone)

Applied separate granulation process to improve dissolution

* Gelling tendency of Losartan K (in gastric pH) influence on the disso. of Amlodipine
Losartan accelerates the degradation of Amlodipine (oxidative reaction)

- Screened stabilizer, added anti-oxidant to the formulation to overcome this chemical interaction.
Spray drying - antioxidant

Wet granulation

Losartan K

High dense compacted granules

Mixed granules

Formulation concept & manufacturing process related patents (4)

1. KR 1247583 Combination composition (disso)
2. KR 1160151 Combination composition (disso)
3. KR 1232296 Combination composition (stability)
4. KR 2009-0005840A Combination composition

3 granted
1 published
Clinical study overview

- Safety
  - Ph 1 DDI
  - Ph 1BE (FDC vs co-admin. of RLD)
- Efficacy
  - Ph 2 Dose finding
  - Ph 3 Efficacy

2.7 years for whole clinical study
Quite short, compared to NCE products
June, 2009 : Launched in Korea (Co-marketing with MSD)
Amosartan & Cozzar XQ & Amzzar

- Total sales was increased steadily up to 70M USD in Korea (2014)
- Expect, export to more than 50 countries
  - Launched in Russia, Columbia, Panama, Malaysia, Turkmanistan…..
  - Waiting for an approval from countries in east/mid asia, mid-America, Africa…..
2-2. Bi-layer tablet
- Rovelito® tablet.
- One of the most ideal combination for a treatment of accompanying disease of hypertension and hyperlipidemia.

**Aprovel (Irbesartan 150, 300mg)**

**Lipitor**
(atorvastatin 10, 20, 40, 80mg, Ca)
No chemical interaction between APIs

basic stabilizer for atorva. influence to the stability of Irbesartan

Need to prevent the interaction between Irbesartan & basic stabilizer

Imp. B of Irbesartan, 40°C, 75% RH

- Basic stabilizer

Acceptable criteria
The formulation concept of Rovelito is Bi-layer, to separate irbesartan from basic stabilizer.

- By making a bi-layer tablet, stability was improved and meet the acceptable criteria under 6month accelerated condition.
Different granulation for each layer

* Applied different granulation, considering physiochemical properties & target release profile of each API

Atorvastatin

- Fluid Bed Granulation - rapid dissolution

Irbesartan

- High Shear Granulation - High density granule

**Fluid Bed Granulation**

- Water 900mL, paddle, 50rpm
  
  ![Graph showing dissolution for Atorvastatin with f2: 88.2](#)

**High Shear Granulation**

- 0.1N HCl 1000mL, paddle, 50rpm
  
  ![Graph showing dissolution for Irbesartan with f2: 62.1](#)

→ Obtained similar dissolution profiles to that of each RLD
Considering de-lamination

* De-lamination can happen in bi-layer tablet (During Compression, Coating, Packaging, Shipping, Storage)

Caused by
1. Insufficient interlocking in the interfacial area  
   ➞ high interfacial surface area & roughness in the adhesion surface
2. Different thermal expansion of each layer  
   ➞ similar excipient to each layer is better
3. Air entrapment between layers during compression

Preventing delamination issue

<table>
<thead>
<tr>
<th>Formulation consideration</th>
<th>Sufficient amount of binder, Minimum amount of lubricant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Utilize excipient which has large surface area (silicone dioxide)</td>
</tr>
<tr>
<td></td>
<td>Similar excipients was applied to each layer</td>
</tr>
</tbody>
</table>

| During Compression          | 1st Layer: minimum compression force  
   ➞ increase roughness of interfacial layer |
|----------------------------| 2nd Layer: increased dwell time for main compression  
   ➞ prevent air entrapment between layers |

International Journal of Pharmaceutics 452 (2013) 249–256
Manufacturing process [Rovelito]

- **Irbesartan 1st Layer**
  - Weighing
  - Granulation (HSM)
  - Drying/Sizing
  - Blending

- **Atorvastatin 2nd Layer**
  - Weighing
  - Granulation (FBG)
  - Drying/Sizing
  - Blending

- **Uncoated**
  - Atorvastatin Ca
  - Irbesartan

- **Film coated**
  - 150/10mg
  - 150/20mg

- **Formulation concept & manufacturing process related patents (3)**
  1. KR 1248804 - Combination composition (bi-layer)
  2. KR 2012-0096036A - Combination composition (process)
  3. KR 2012-0096477A - Combination composition (stability)

  1 granted
  2 published
Rovelito, a treatment of accompanying diseases

- Ph2 clinical study was not required to get an approval
Dec. 2013, Launched in Korea (Co-promotion with Sanofi)
Total sales is gradually increased by year
& expect to reach more than 50mil USD.
Innovations in development

2-3. PolyCap capsule
- Montelizin® capsule
- Dutams® capsule
Levocetirizine 2HCl → Histamine H1 receptor antagonist

Montelukast Na → Leucotriene D4 antagonist → Histamine H1 receptor antagonist

One of the most ideal combination of drugs for a treatment of accompanying disease of allergic rhinitis & asthma

- Montelukast Na + Levocetirizine 2HCl
  - 2 strengths
  - 10/5 (adult), 5/5 (children)
- Treatment for allergic rhinitis & asthma

Singulair (montelukast 10mg, Na)

Xyzal (levocetirizine 2HCl 5mg)
Inter-API interaction

- Levocetirizine has a negative effect to stability of Montelukast.
- Montelukast has a negative effect to stability of Levocetirizine.

have to separate APIs
Monolithic tablet

Bi-Layered Tablet

Polycap: 2T x montelukast, 1T x levocetirizine

Montelukast imp. A

Levocetirizine total imp.

Polycap showed better stability → selected as a dosage form
PolyCap (w tablet) provided lower dissolution rate → result in delayed PK profile in dog → tried to improve dissolution rate
MUST technology

- Abbreviation for Multi Unit Spheroidal Tablet
- Unique and innovative technology for FDC product

MUST concept

- PolyCap of mini spheroidal tablets
  (with diameter of less than 2mm)

Characters

- Combined characters of Polycap + MUPS
  - Prevent interactions
  - Make FDC more easily
  - Adjust a dose by changing the number of tablets
  - Expect lower PK variability
  - Expect narrow gastric emptying time
  - Expect rapid dissolution
dissolution rate was improved, and showed similar profiles to each RLD
PolyCap filling machine for (mini)tablet

Max capacity
: more than 100,000 caps/h
Coating

Encapsulation

FB coating

Montelukast Na mini tablet

Compression (specified punch)

& Fluidbed coating

Levocetirizine 2HCl Mini tablet

Formulation concept & manufacturing process related patents (3)

<table>
<thead>
<tr>
<th></th>
<th>KR</th>
<th>Description</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1418404</td>
<td>Combination composition (MUST)</td>
<td>1 granted</td>
</tr>
<tr>
<td>2</td>
<td>2011-0070680A</td>
<td>Combination composition (PolyCap)</td>
<td>2 published</td>
</tr>
<tr>
<td>3</td>
<td>2013-0075099A</td>
<td>Combination composition (Stability)</td>
<td></td>
</tr>
</tbody>
</table>
Clinical study

Clinical trial I / III

- DDI, Bioequivalence (BE)
  - Done

Clinical phase I

- Bioequivalence (BE) was proved

Clinical phase III

- On-going
2-4. PolyCap capsule

- Dutams® capsule
- Montelizin® capsule
One of the most ideal combination of drugs for a treatment of BPH

*Benign Prostatic Hypertrophy*

- **Dutasteride**
  - 5-α reductase inhibitor
  - covert testosterone to dehydrotestosterone

- **Tamsulosin HCl**
  - adrenergic receptor blocker
  - relaxation in smooth muscle
  - therefore less resistance to urinary flow

- **Dutasteride** + **Tamsulosin HCl**
  - 0.5mg / 0.4mg

**Avodart (dutasteride 0.5mg)**

**Flomax (tamsulosin HCl 0.4mg)**
Different dosage form / drug release characteristic

- Dutasteride
  Immediate release, soft gelatin capsule of oil formulation

- Tamsulosin HCl
  Sustained release, coated pellet

Development of a one combination dosage form, which overcomes this difference and also is bioequivalent to each RLD

PolyCap
retain each dosage forms / drug release characteristics
* **PolyCap**, dutasteride soft capsule & tamsulosin pellet

**dutasteride soft capsule**
- 6 oblong (same as Avodart)

**tamsulosin pellet**
- Pellet (same as Floma)

- # 00 too big to swallow → size optimization was necessary

→ size reduction of Dutasteride softgel

& amount reduction of Tamsulosin pellet was performed to make a #1 cap.
By changing a formulation ‘from Oil to Oil+surfactant’

- Reduced the size of dutasteride soft capsule ‘from 6 oblong to 2 oval’.

Bioequivalence, small one to big one was proven by human study.
• **Reduced total amount of pellet in half by increasing drug load**
• **Changed manufacturing process**

**Manufacturing of spherical pellet**

1. Extruding
2. Spheronizing
3. Sustained release coating
4. Enteric coating

- Spherical bead (cellulose + API)
  (Like a rotor granulator)
- Coating (Enteric)
Manufacturing process [Dutams]

1. Dutasteride 0.5mg Soft gelatin cap
2. Tamsulosin 0.4mg sustained release Pellet

- Mixing
- Capsuling
- Drying
- Mixing & kneading (HSM)
- Extruding
- Spheronizing
- Drying (Oven)
- Sieving

Formulation concept & manufacturing process related patents (4)

<table>
<thead>
<tr>
<th>No.</th>
<th>Patent Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KR 0582350</td>
<td>Tamsulosin HCl Formulation (Pellet)</td>
</tr>
<tr>
<td>2</td>
<td>KR 2012-0007399A</td>
<td>Dutasteride softgel composition (size reduced)</td>
</tr>
<tr>
<td>3</td>
<td>KR 2013-0075884A</td>
<td>Dutasteride softgel composition (capsule shell)</td>
</tr>
<tr>
<td>4</td>
<td>KR 2014-0187571A</td>
<td>Dutasteride softgel composition (size reduced)</td>
</tr>
</tbody>
</table>

1 granted
3 published
Clinical trial I / III

- Drug-Drug Interaction (DDI)
- Bioequivalence (BE) test
  ➔ On-going

Clinical phase III
  ➔ will take place soon
Part 3. Summary & Conclusion
1. For formulation of FDC, inter-API interaction, compatibility, target dissolution profiles & dosage form size must be considered.

2. Hanmi has various platforms for FDC, such as Monolithic, Bi-layer, Multi-layer coating or Polycap.

3. Especially, the Polycap is an ideal platform for FDC which is possible to retain original dosage form and drug release characteristic, and prevent an interaction between APIs.

4. Based on these platform technologies, Amosartan and Rovelito were successfully commercialized with global companies. Currently, Hanmi still has 8 more developing FDC products for global markets.

→ Hanmi believes that FDC is a highly value-added product which has much of benefits to patients and companies.
Thank you