Compritol® 888 ATO
The Smart Strategy for Sustained Release Formulation
• Introduction
• Compritol 888 ATO: Product overview
• Compritol 888 ATO: Product properties
• Formulating SR Tablets with Compritol 888: Gattefossé Strategy
• How to Modulate Release Profiles: Key Parameters
• Lipidic Matrix Performance
• Conclusion
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GATTEFOSSÉ FUNCTIONAL EXCIPIENTS

OLEOCHEMISTRY ➞ Gattefossé excipients are made by esterification

Alcohols ➜ Fatty acids

LIPIDS ➞

Esters of glycerol, PEG esters, Propylene glycol esters, Polyglycerol esters

FUNCTIONAL EXCIPIENTS
THE GATTEFOSSÉ LIPID FAMILY

Partial glycerides
- More lipophilic
  - Oily vehicle
  - Solubilizer
  - Sustained release agent
  - Taste-masking agent

Polyalcohol esters
- Co-surfactant
- Solubility enhancers

Polyoxylglycerides
- More amphiphilic
  - Solubilizer
  - Surfactant

All products are derived from vegetable oils and fats

MELTING POINT

HLB
PHARMACEUTICAL SOLUTIONS

FUNCTIONAL EXCIPIENTS

Liquid

Solid

Semi-solid

Oral route

Dermal route

Rectal/Vaginal route
### ORAL APPLICATIONS

**Which functionality? which product? which process**

#### Sustained Release

**Excipients**  
- Compritol 888 ATO  
- Precirol ATO 5  
- Gelucire 39/01 - 43/01

**Process**  
- Compression  
- Capsule filling  
- Melt granulation & pelletization  
- Spray cooling / Prilling

**Final dosage forms**  
- Tablet  
- Capsule  
- Granule/Pellet (Sachet / Capsule)

#### Bioavailability Enhancement

**Excipients**  
- Gelucire 44/14  
- Gelucire 50/13  
- Labrasol  
- Labrafils  
- See list of excipient for SEDDS or SMEDDS

**Process**  
- Capsule filling  
- Adsorption / Compression  
- Melt granulation & pelletization

**Final dosage forms**  
- Capsule  
- Tablet  
- Granule/Pellet (Sachet / Capsule)
WHY SUSTAIN DRUG RELEASE?

- Reduced frequency (short half life drugs)
- Reduced side effects (no plasma concentration peaks)
- Improved efficacy (steady state)
- Improved patient compliance (intake once or twice a day)
- Extension of patent life (life cycle management)
APPROACHES TO SUSTAINED DRUG RELEASE

Film coating on drug loaded carriers
- Water soluble polymers – e.g. PVA
- Water insoluble polymers - e.g. EC
- pH-dependent polymers – e.g. aminoethyl methacrylate copolymer

Drug embedded in a matrix
- Hydrophilic matrix – e.g. HPMC
- Hydrophobic matrix – e.g. EC
- Lipophilic matrix – e.g. glycercyl dibehenenate (Compritol 888 ATO)
APPROACHES TO SUSTAIN DRUG RELEASE

Structural matrix
- non-erodible
- non-swelling

Swelling matrix
- swelling over time

Eroding matrix
- continuous surface erosion

from Prof Sandra Klein – Greifswald University (GER)
Reproducible sustained release matrix systems rely on an infinite matrix network which entraps drug and prevents its immediate release*

WHY LIPIDIC MATRIX FOR SUSTAINED RELEASE?

No solvent needed to disperse the lipid

Atomized powder for direct compression, wet granulation, etc.

Drug release kinetics not influenced by pH changes

Avoid burst release effect

Bypass patents of hydrophilic SR matrix
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**Glyceryl behenate**

USP-NF/EP/ChPh
GRAS, FDA IIG,
acceptable non-medicinal ingredients (Canada)

**MP = 70° C, HLB = 2**

Atomized *spherical* particles
D50 = 56.92 ± 1.63 µm
(n=69 batches)

*Non-erodable* matrix

Use level: **15 to 50%**
More than 50 years of use in pharmaceutical tablets

<table>
<thead>
<tr>
<th>API</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertaconazole</td>
<td>Antifungal</td>
</tr>
<tr>
<td>Tilidine</td>
<td>Analgesic</td>
</tr>
<tr>
<td>Metformin</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Glicazide</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Prazocin hydrochloride</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Felodipin</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Anti-epileptic</td>
</tr>
<tr>
<td>Ropinirole hydrochloride</td>
<td>Anti-Parkinsons</td>
</tr>
<tr>
<td>Methylxanthine</td>
<td>Anti-Parkinsons</td>
</tr>
</tbody>
</table>
THERMAL CHARACTERISTICS

Thermorheogram

Melt & Crystallization DSC Curve
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A MULTI-FUNCTIONAL EXCIPIENT

Lubricant

*tablet compression*

Taste masking

*HMC, spray cooling, melt granulation*

Sustained release

*HMC, spray cooling, granulation, extrusion*

**Processing flexibility!**
CHEMICALLY INERT

Compatible with other functional excipients
   Compatible with APIs, HPMC, Carbomers, PVP, etc

Compatible with all APIs
   Unlike e.g. HPMC in combination with reactive drugs (salts and acids) or excipients*
   Impact on long term stability/drug release kinetics

* Wells et al., 2010, AAPS Pharmascitech 11, 113-119
Taste masking attribute
masks the taste using melt processes
Reduced risk of dose dumping

- non-ionic, functionality un-affected by pH changes
- matrix does not dissolve in ethanol
- melt process increases matrix resistance
**Draft Guidance on Bupropion Hydrochloride from FDA:**

“Due to concerns of dose dumping from this drug product when taken with alcohol, please conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium”

**Ingredient**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>DC % w/w</th>
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</thead>
<tbody>
<tr>
<td>Bupropion HCl</td>
<td>33.3</td>
</tr>
<tr>
<td>Compritol 888 ATO</td>
<td>30.3</td>
</tr>
<tr>
<td>DCPA</td>
<td>22.3</td>
</tr>
<tr>
<td>Lactose</td>
<td>11.1</td>
</tr>
<tr>
<td>Compritol 888 ATO</td>
<td>3</td>
</tr>
</tbody>
</table>

Dissolution studies in hydroalcoholic media are recommended by the FDA.

Bupropion HCl lipid matrices show no evidence of EtOH-associated dose dumping.
NON-DIGESTIBLE

Resistant to physiological conditions
- non-digestible by digestive enzymes present throughout the GI tract
- protects from physiological conditions and favours consistent drug release

PROCESSING FLEXIBILITY STRATEGY

Hydrophilic matrix
DC only, no WG unless with *organic solvent*

Hydrophobic matrix
DC only

Lipophilic matrix

- **Direct compression**  
  *drug, Compritol, diluent, lubricant*

- **Wet granulation**  
  *DC + aqueous binder solution*

- **Melt granulation**  
  *partial melting of Compritol*

- **Solid dispersion**  
  *drug dispersed in Compritol melt*

**Solvent-free Processes!**
OTHER PROCESSES

Spray cooling ✓
Hot melt coating ✓
Hot melt extrusion ✓
Solid lipid nanoparticles ✓
Physical mixture

When both active and lipid excipient are solid powders, creation of a lipid barrier around the drug particle by blending and compression
DIRECT COMPRESSION
WET GRANULATION

Step 1:

Compritol® ATO 888  API

Step 2:
**HOT PROCESS**

**Solid dispersion/solution**

Dispersion/solution of the drug in the carrier

*Heat is generally involved*

1. **Solid drug particles**
2. **Drug added to molten lipid**
3. **Suspension or solution**

Apply Heat
Melt granulation should be considered when API > C888
Extrusion can be done at T°C below lipid melting point i.e. 60°C
NO limit in viscosity even when API<C888
Possibility to do melt granulation
(AAPS poster 2012 from Justin Keen –Austin university TX)
MELT GRANULATION

Thermoplastic granulation

- Lipid Excipient powders or pellets
- Solid drug particles
- One step process
- no solvents
- time and cost efficiency

High Shear mixer
Heating

GRANULATION STEP

Liquid to solid bridge

SPHERONISATION STEP

Granules

Pellets
CASE STUDY # 1: SR THEOPHYLLINE TABLET

Theophylline dissolution profiles in pH 4.5 from tablets containing 15% theophylline / 15% Compritol 888 ATO / QS std excipients
CASE STUDY # 1: SR THEOPHYLLINE TABLET

Theophylline dissolution profiles in pH 4.5 from tablets containing 15% theophylline / 15% Compritol 888 ATO / QS std excipients

![Graph showing theophylline dissolution profiles](image)

- **Tablet at $t_0$**
- **Tablet after 24h**
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# LIPID MATRIX SR TABLET COMPOSITION

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Active ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>MATRIX FORMER</td>
<td><em>Compritol 888 ATO</em></td>
</tr>
<tr>
<td>DILUENT (co-excipients)</td>
<td>Tablet size, flow, compression</td>
</tr>
<tr>
<td></td>
<td><em>(lactose, MCC, DCPA...)</em></td>
</tr>
<tr>
<td>LUBRICANT (0.5 – 3%)</td>
<td>Glidant, anti-adhesion, anti-friction</td>
</tr>
<tr>
<td></td>
<td><em>(Compritol 888 ATO, talc, Mg stearate...)</em></td>
</tr>
</tbody>
</table>
Several **parameters** impacting dissolution/release profile:

- Amount of **SR matrix** *(drug vs. SR matrix ratio)*
- Amount and nature of **diluents** selected
- Tablet **size** *(diffusion path-length)*
- **Processing** route *(cold vs hot)*
Theophylline release of matrix tablets prepared by direct compression.

900mL phosphate buffer pH 4.5, 75 rpm, 37°C

**INCREASE Compritol content**

**DECREASE drug release**

*easy to modulate*

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>0% C888 % w/w</th>
<th>20% C888 % w/w</th>
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</thead>
<tbody>
<tr>
<td>Theophylline</td>
<td>16.7</td>
<td>16.7</td>
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<tr>
<td>Compritol 888 ATO</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>DCPA</td>
<td>52.9</td>
<td>39.5</td>
</tr>
<tr>
<td>Lactose</td>
<td>26.4</td>
<td>19.8</td>
</tr>
<tr>
<td>Mg Al metasilicate</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Mg Stearate</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**INCREASE Compritol content**

**DECREASE drug release**

*easy to modulate*
CHOICE OF DILUENTS

Lactose  ⇒  water soluble, good compressibility and flowability, low hygroscopicity, physicochemical stable, cost effective

MCC  ⇒  water insoluble, disintegration properties (swelling), compressible, rather good flowability

DCPA  ⇒  water insoluble, slightly alkaline (pH 7 – 7.4), good compressibility and flowability, sticking to the die

Sucrose, starch, mannitol, ethylcellulose, HPC ...

Modulation also provided by combining various diluents
The nature (and the amount) of diluent plays an important role in the modulation of release rate.
## Impact of Compression Forces

### Ingredients

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>%</th>
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<tbody>
<tr>
<td>Theophylline</td>
<td>20</td>
</tr>
<tr>
<td>C888 ATO</td>
<td>15</td>
</tr>
<tr>
<td>Fujicalin SG</td>
<td>32.25</td>
</tr>
<tr>
<td>Tablettose 80</td>
<td>32.25</td>
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<tr>
<td>Mg stearate</td>
<td>0.5</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Run #</th>
<th>Compression force (kN)</th>
<th>Pre-compression force (kN)</th>
<th>Compression speed (rpm)</th>
<th>Feed rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run 1</td>
<td>5.0</td>
<td>1.0</td>
<td>30.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Run 4</td>
<td>25.0</td>
<td>1.0</td>
<td>30.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Run 5</td>
<td>15.0</td>
<td>1.0</td>
<td>30.0</td>
<td>6.0</td>
</tr>
</tbody>
</table>
IMPACT OF COMPRESSION FORCES

14mm tablets

12mm tablets
The tablet dimension can be an appropriate tool to adjust drug release kinetics.
IMPACT OF PROCESSING ROUTE

a) Niacin

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity (%)</th>
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<tbody>
<tr>
<td>Niacin</td>
<td>50</td>
</tr>
<tr>
<td>Compritol® 888 ATO</td>
<td>30</td>
</tr>
<tr>
<td>Povidone</td>
<td>5</td>
</tr>
<tr>
<td>Lactose</td>
<td>14.5</td>
</tr>
<tr>
<td>Mg stearate</td>
<td>0.5</td>
</tr>
<tr>
<td>Tablet weight</td>
<td>1000 mg</td>
</tr>
</tbody>
</table>

Drug release (%)

- Direct compression
- Wet granulation
- Hot melt extrusion

Time (h)

Cold process

Hot process
Reduced wettability compared with cold processed tablets

Contact angle of a water droplet on the tablet surface

Water soluble

Compritol® 888
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TRANSFERABILITY: SCALE-UP

- excenter vs rotary press
  - direct compression
- small vs high quantity
  - solid dispersion

**Theophylline**
- Lab scale vs Pilot scale

**Metoprolol succinate**
- Lab scale vs Pilot scale
MIS-HANDLING: BUPROPION HCL

Splitting or damage to an SR tablet may affect the drug release profile leading adverse effects

Compritol matrix

Zyban LP 150mg

Product label Wellbutrin® SR/XL (bupropion HCl) states that tablets should be taken whole and that splitting could lead to adverse effects. Wellbutrin® is registered trademark of GlaxoSmithKline Ltd.

Zyban® is registered trademark of GlaxoSmithKline Ltd.
MIS-HANDLING: BUPROPION HCL

Bupropion HCl case study

Zyban® is registered trademark of GlaxoSmithKline Ltd.

Compritol matrix = SR unaffected
no accidental dose dumping if tablet is broken
IN-VIVO EFFICACY - THEOPHYLLINE

Mean cumulative theophylline absorbed in 8 beagle dogs


Table: Ingredients %w/w

<table>
<thead>
<tr>
<th></th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Compritol 888</td>
<td>30</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbomer</td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>HPMC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>Spray-dried lactose</td>
<td>20</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCPA</td>
<td>50</td>
<td></td>
<td></td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>MCC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
</tr>
</tbody>
</table>

Tablet weight 200 mg made by direct compression

Gattefosse
In vitro metoprolol succinate release from lipid matrix closely matches market references.
1- The plasma concentration time profile of Compritol tablet and MetXL50 is comparable

2- The R² values in the IVIVC indicates excellent correlation

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Performance & flexibility

- Compatible with all processing routes
- Flexible release profile tailoring
- No organic solvent
- pH- and ethanol-independent

Global regulatory acceptability

- Pharmacopoeia, GRAS
- Well characterized

Patent opportunities
## Glyceryl Behenate in Approved Dosage Forms

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Matrix / drug delivery technology system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ropinirole</td>
<td>Multilayered / controlled release DDT</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Multi-layer / core timed release DDT</td>
</tr>
<tr>
<td>Tilidine</td>
<td>Matrix tablet</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Matrix tablet</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Matrix tablet</td>
</tr>
<tr>
<td>Metformin HCL</td>
<td>Matrix tablet</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>Multilayered / controlled release DDT</td>
</tr>
<tr>
<td>Zileuton</td>
<td>Multilayered / controlled release DDT</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Microgranules</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Matrix tablet</td>
</tr>
<tr>
<td>Azithromicine</td>
<td>Coated microgranules / suspension</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Matrix tablet</td>
</tr>
<tr>
<td>Guanfacine HCl</td>
<td>Matrix tablet</td>
</tr>
</tbody>
</table>
Investigated drugs
- Metoprolol succinate
- Metformin HCl
- Theophylline
- Buproprion HCl
- Diclofenac sodium
- Ketoprofen
- Niacin
- Felodipine

Preparation techniques
- direct compression (DC)
- wet granulation (WG)
- solid dispersion (SD)
- melt extrusion (HME)

Performance & troubleshooting
- in vitro-in vivo correlation
- curing
- long term storage
- pH-/ethanol robustness
- other case studies
Thank you!
STORAGE STABILITY

Theophylline - direct compression

-Theophylline released over time (h) at different storage periods:
-1 month
-3 months
-6 months
-12 months
-24 months

Diclofenac Na – solid dispersion

-Diclofenac Na released over time (h) at different storage periods:
-11 months
-6 months
-3 months
-1 month
-before storage

Tablets stored in ICH conditions: 25°C, 60% relative humidity