GATTEFOSSÉ

Compritol® 888 ATO

The Smart Strategy for Sustained Release Formulation

People make our name

PRESENTATION CONTENTS

- 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

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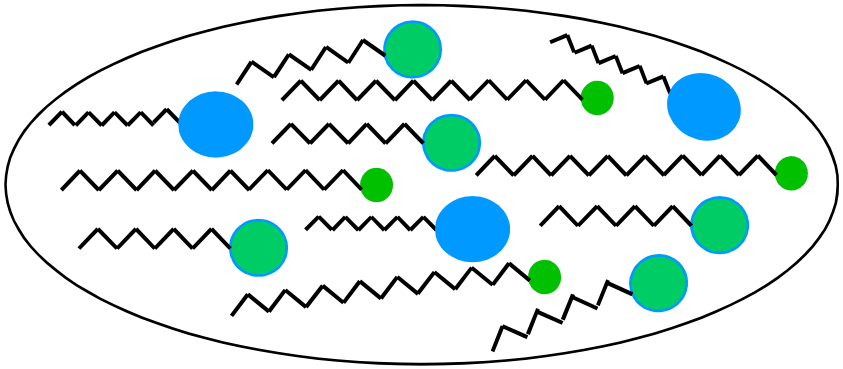
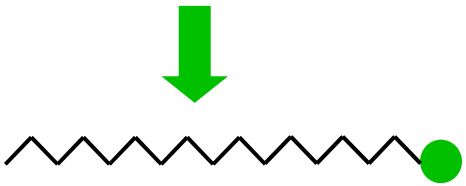
THE GATTEFOSSÉ LIPID FAMILY

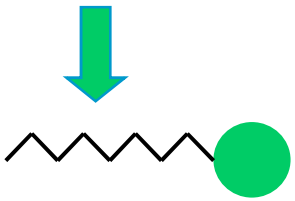


All products are derived from vegetable oils and fats



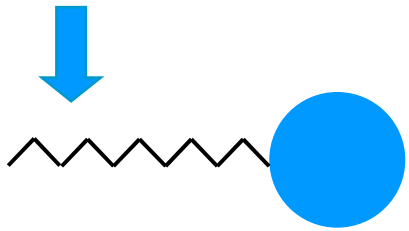
Partial glycerides
More lipophilic

- Oily vehicle
- Solubilizer
- Sustained release agent
- Taste-masking agent



Polyalcohol esters

- Co-surfactant
- Solubility enhancers



Polyoxylglycerides

More amphiphilic

- Solubilizer
- Surfactant

MELTING POINT

HLB

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PHARMACEUTICAL SOLUTIONS

FUNCTIONAL EXCIPIENTS

Liquid

Solid

Semi-solid

Oral route

Dermal route

Rectal/Vaginal route

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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)

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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)

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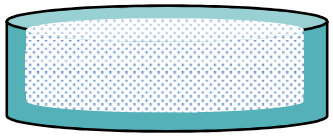
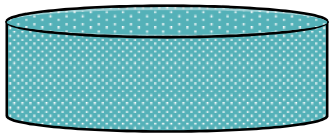
APPROACHES TO SUSTAINED DRUG RELEASE

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. glyceryl dibehenate (Compritol 888 ATO)

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APPROACHES TO SUSTAIN DRUG RELEASE

Structural matrix

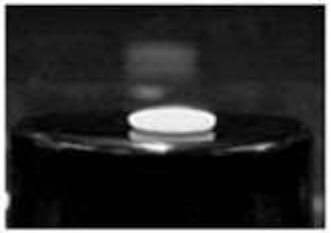
- non-erodible
- non-swelling

Swelling matrix

- swelling over time

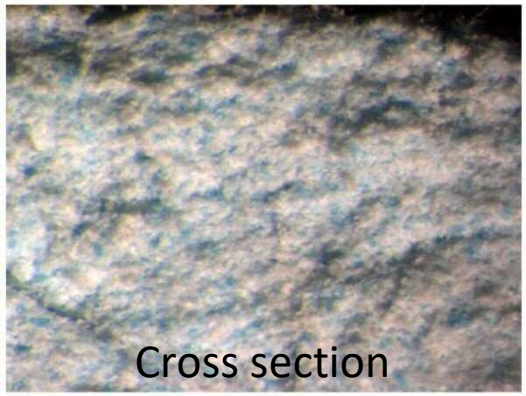
Eroding matrix

- continuous surface erosion



from Prof Sandra Klein – Greifswald University (GER)

COMPRITOL REPARTITION



Reproducible sustained release matrix systems rely on an infinite matrix network which entraps drug and prevents its immediate release*

*Millan M. et al., Pharm. Res. 15 (2) (1998) 220–224

WHY LIPIDIC MATRIX FOR SUSTAINED RELEASE?

No solvent needed to disperse the lipid

~~*Drying step*~~

~~*Organic vapor*~~

~~*Risk of API hydrolysis*~~

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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PRODUCT OVERVIEW

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%

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PRECEDENCE OF USE

- More than 50 years of use in pharmaceutical tablets

API	Indication
Sertaconozole	Antifungal
Tilidine	Analgesic
Metformin	Hypoglycemia
Glicazide	Hypoglycemia
Metoprolol	Hypertension
Nisoldipine	Hypertension
Prazocin hydrochloride	Hypertension
Felodipin	Hypertension
Prednisone	Anti-inflammatory
Diltiazem	Anti-inflammatory
Gabapentin	Anti-epileptic
Ropinirole hydrochloride	Anti-Parkinsons
Methylxanthine	Anti-Parkinsons

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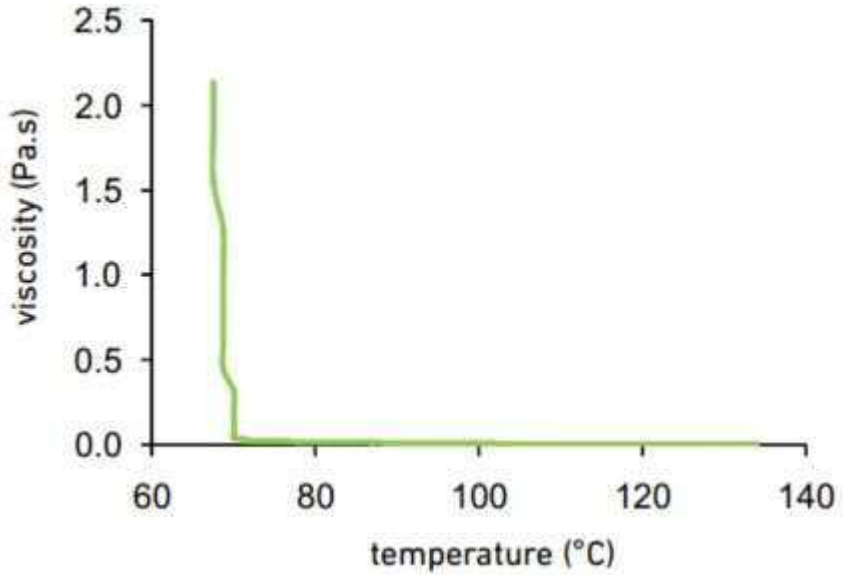
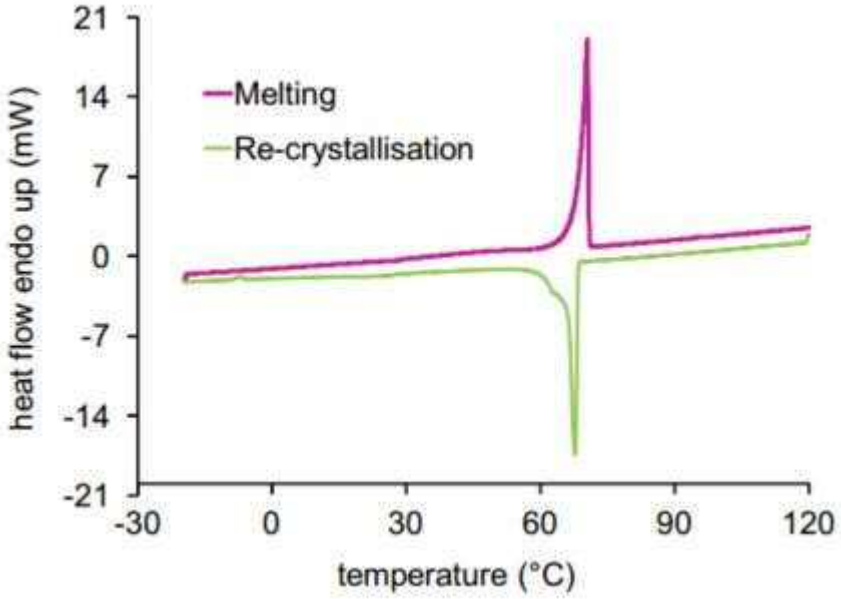
Not an exhaustive list

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!

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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

NEUTRAL IN FLAVOR

Taste masking attribute

masks the taste using melt processes

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PH/ETHANOL INDEPENDENT

Reduced risk of dose dumping

- non-ionic, functionality un-affected by pH changes
- matrix does not dissolve in ethanol
- melt process increases matrix resistance

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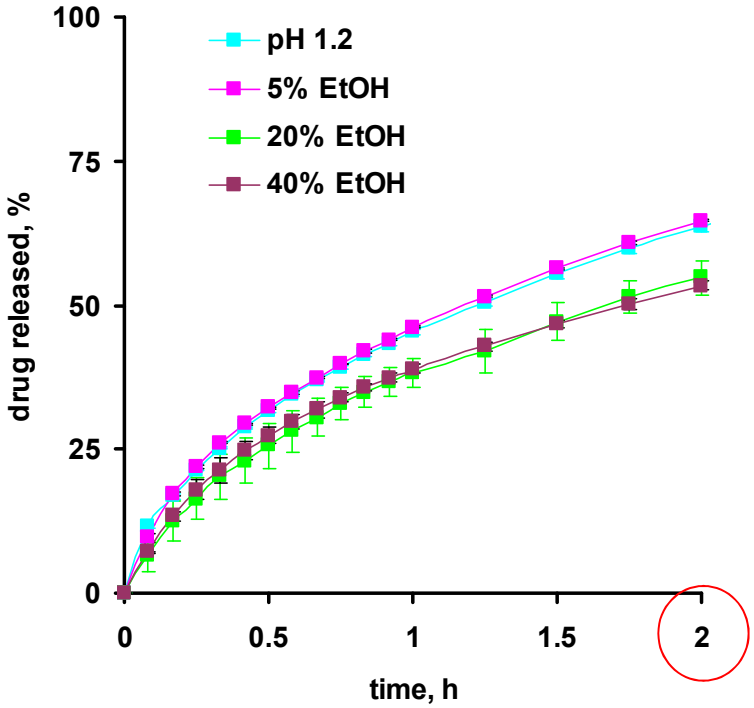
PH/ETHANOL INDEPENDENT

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	DC % w/w
Bupropion HCl	33.3
Compritol 888 ATO	30.3
DCPA	22.3
Lactose	11.1
Compritol 888 ATO	3

Dissolution studies in hydroalcoholic media are recommended by the FDA.

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

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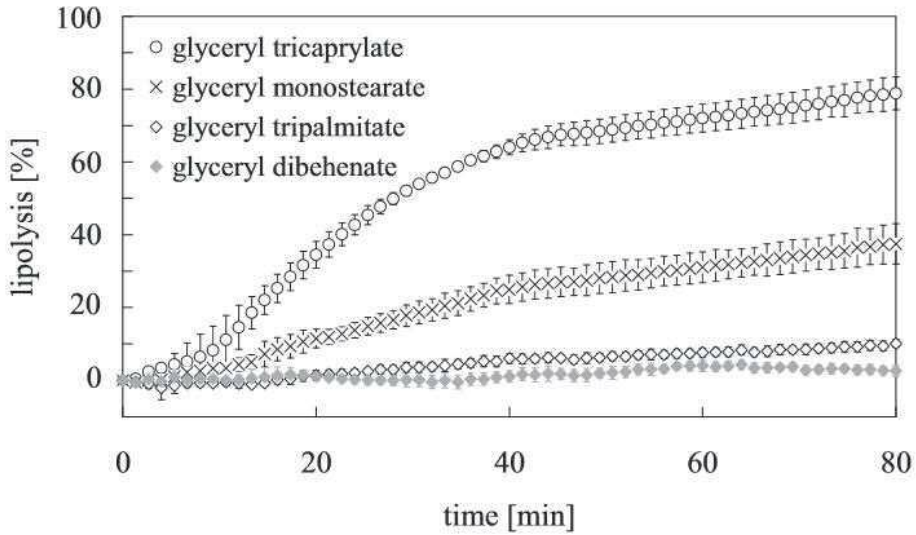
NON-DIGESTIBLE

Resistant to physiological conditions

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



Witzleb R. et al., 2012, Int. J. Pharm. 422, 116-124.

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!

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OTHER PROCESSES

Spray cooling ✓

Hot melt coating ✓

Hot melt extrusion ✓

Solid lipid nanoparticles ✓

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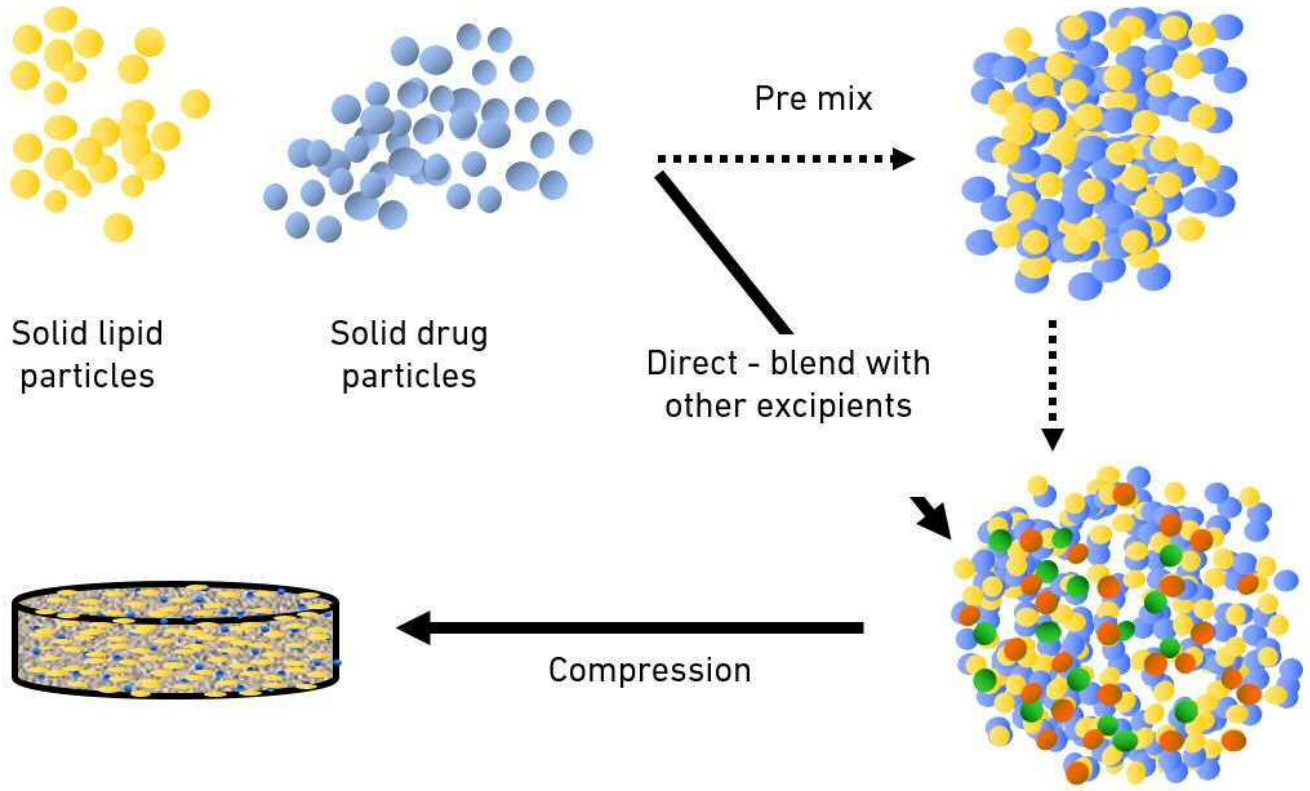
COLD PROCESS

Physical mixture

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



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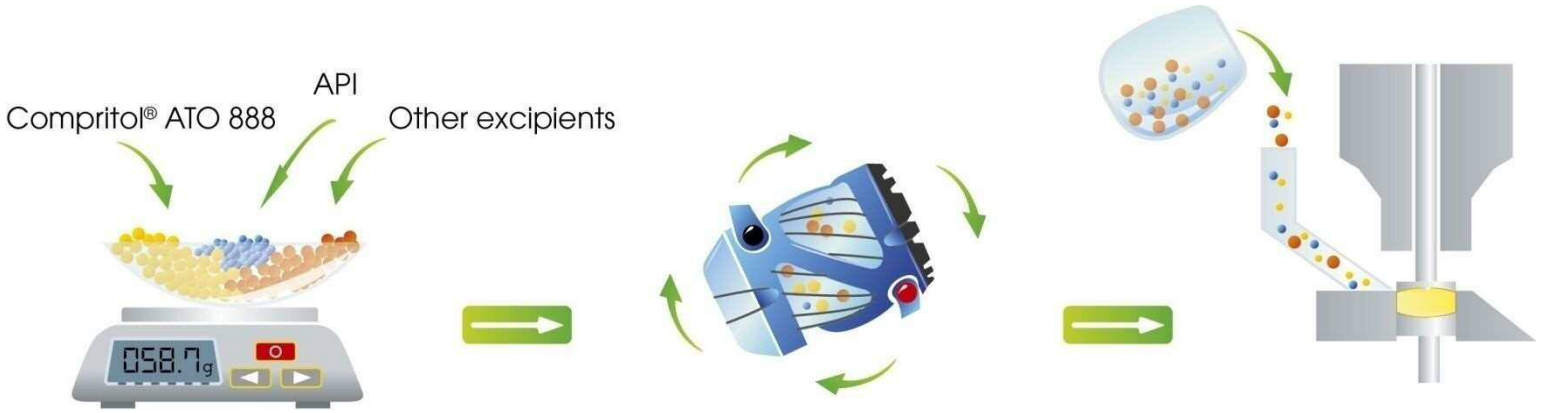
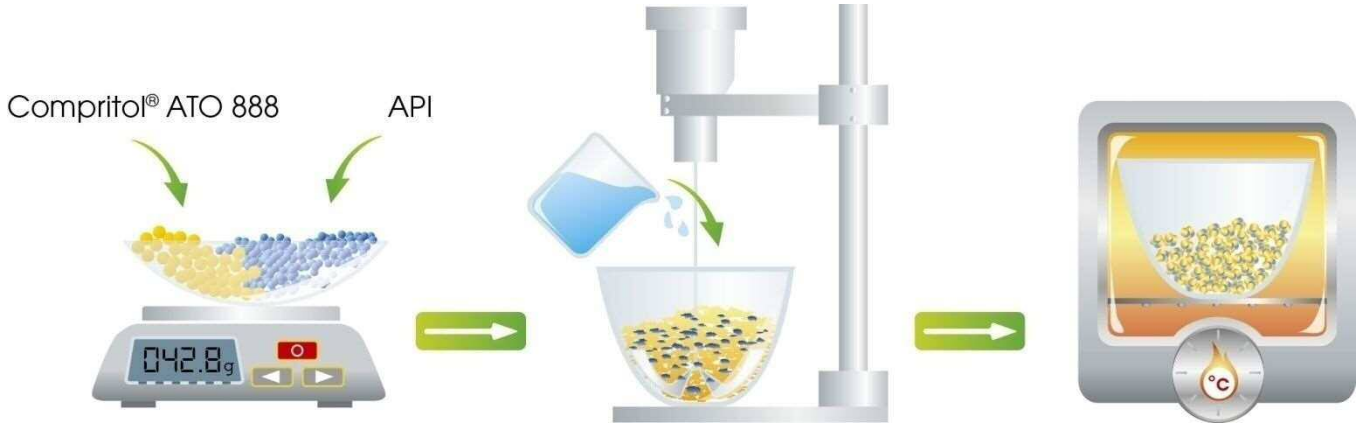
DIRECT COMPRESSION

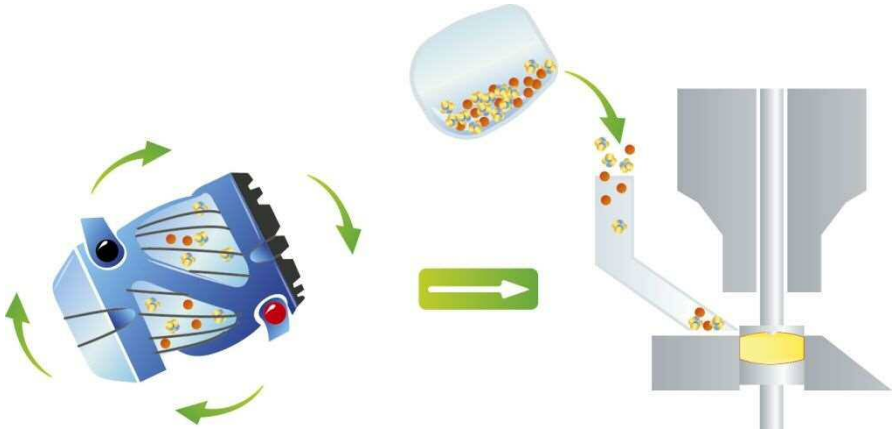


WET GRANULATION

Step 1 :



Step 2 :

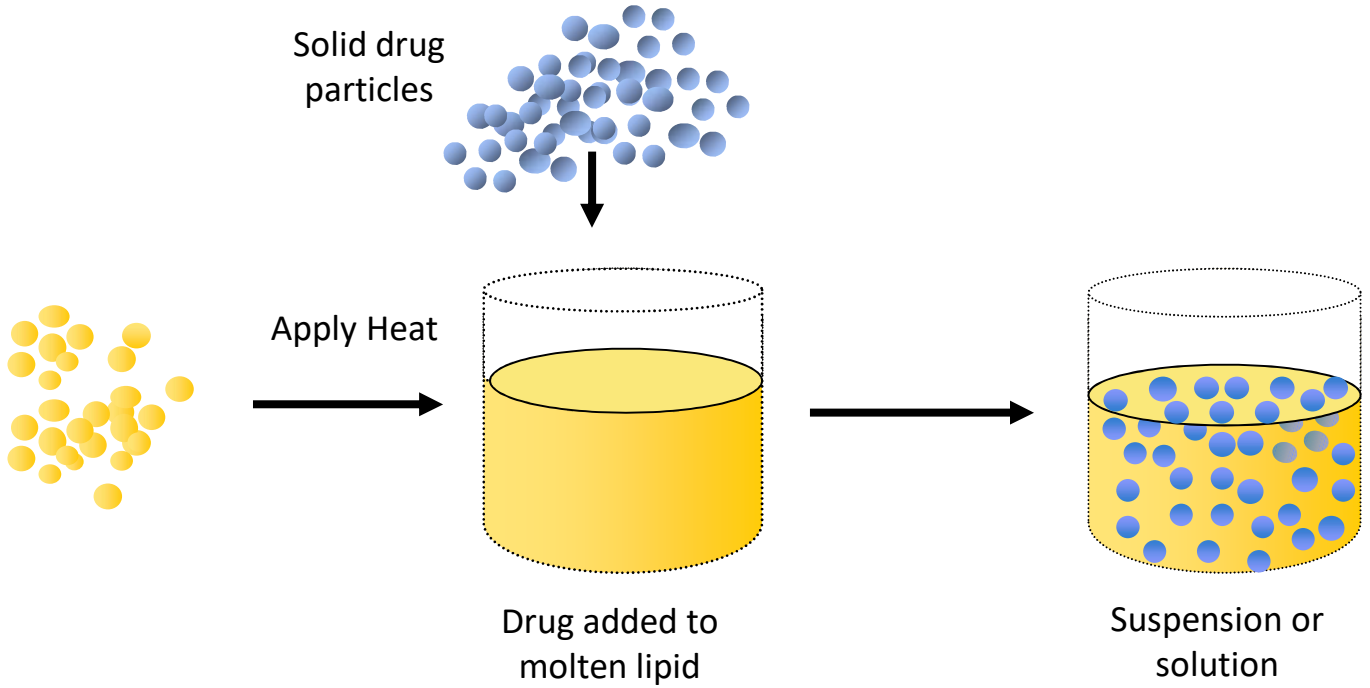


HOT PROCESS

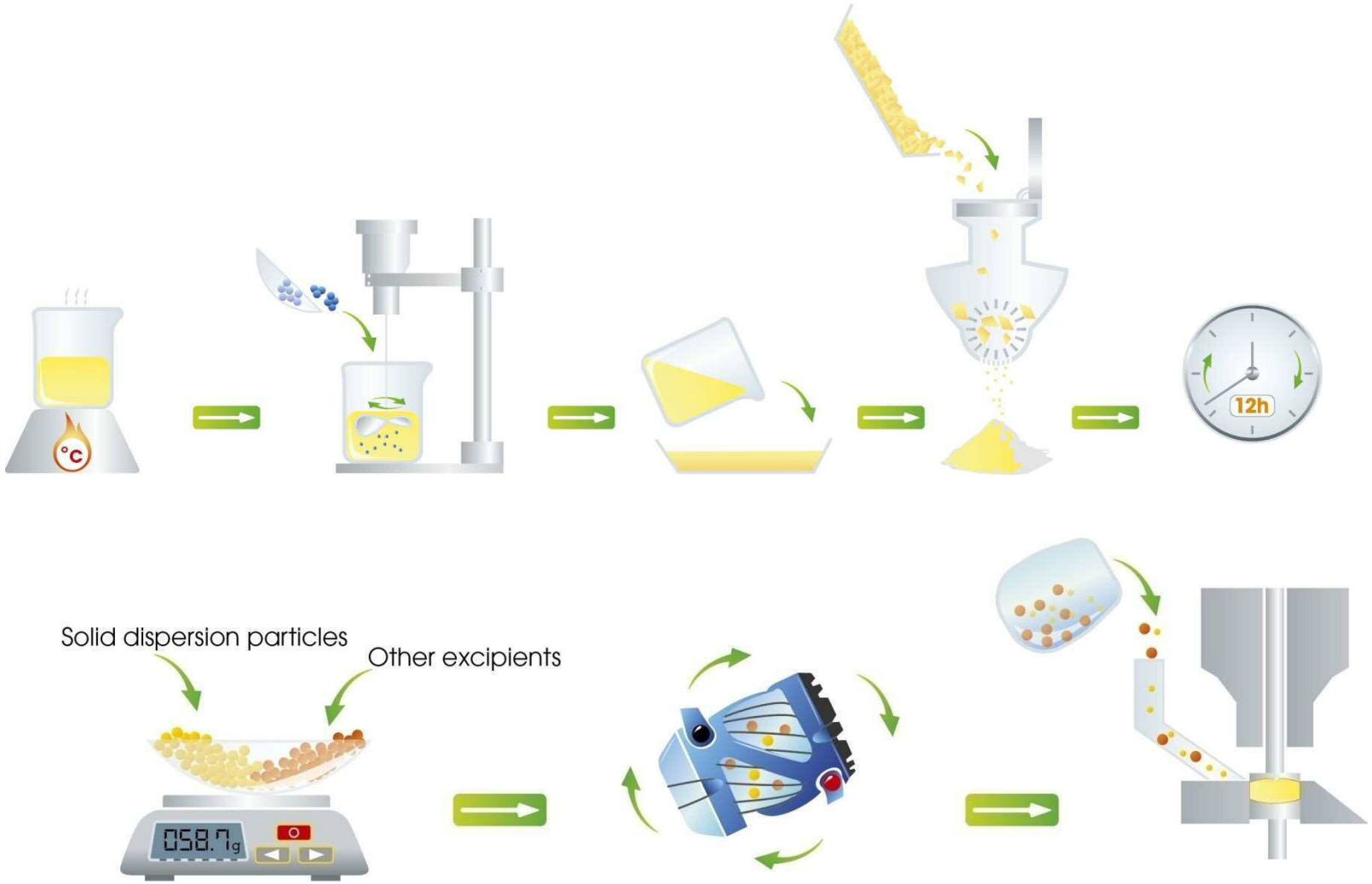
Solid dispersion/solution

Dispersion/solution of the drug in the carrier

Heat is generally involved



MELT & MIX METHOD



Melt granulation should be considered when API>C888

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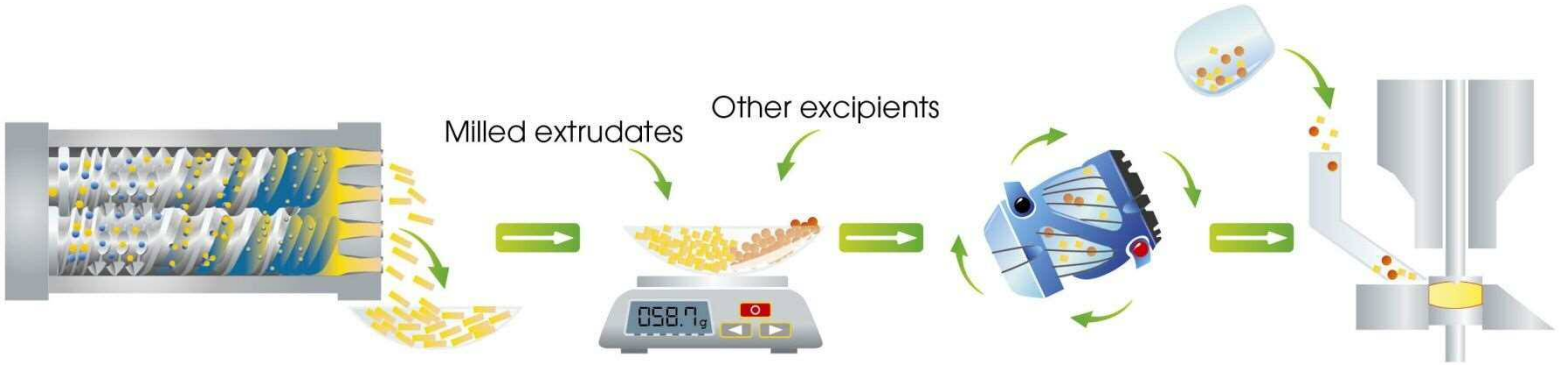
HOT MELT EXTRUSION



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)

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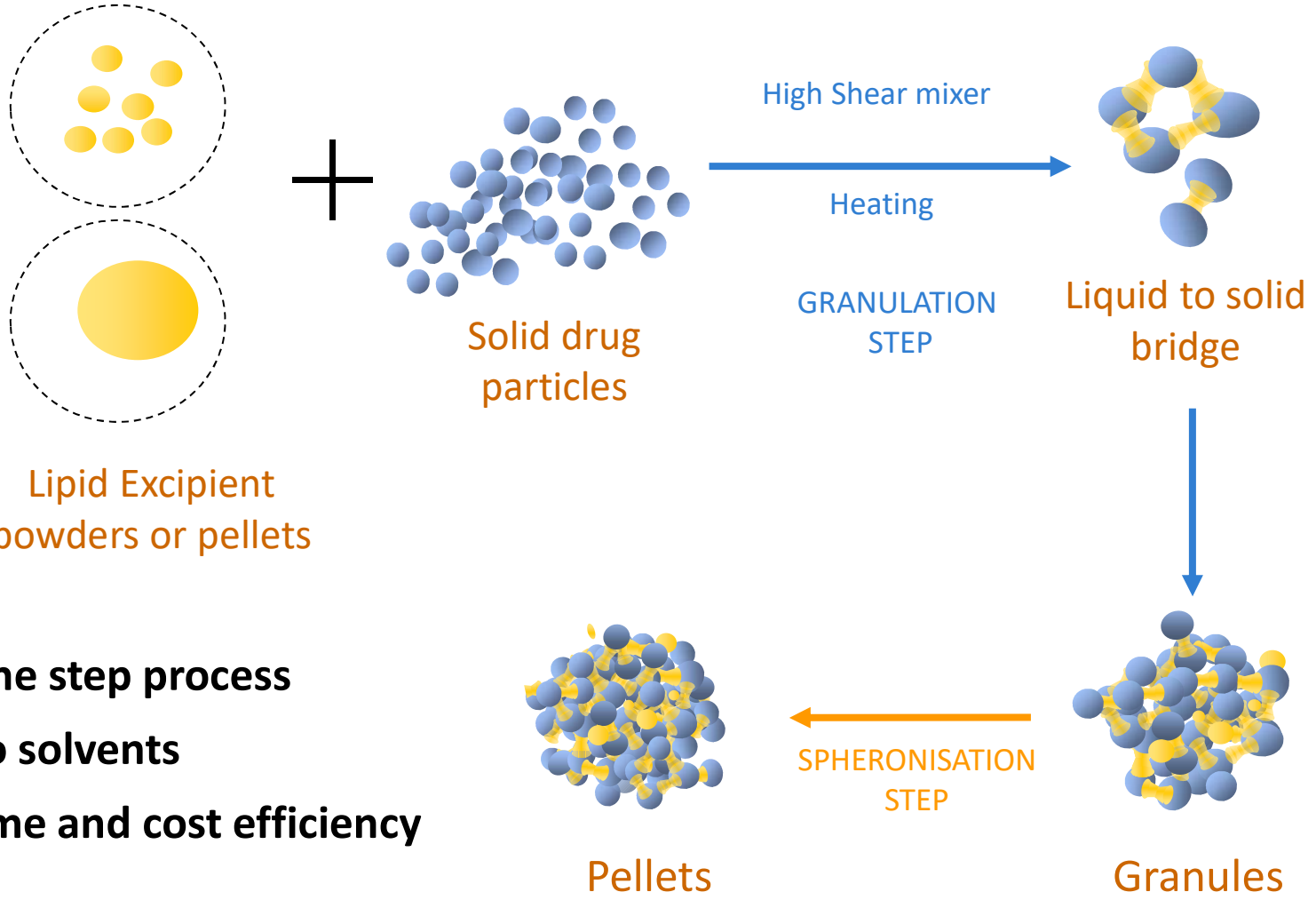
MELT GRANULATION

Thermoplastic granulation



One step process

no solvents

time and cost efficiency

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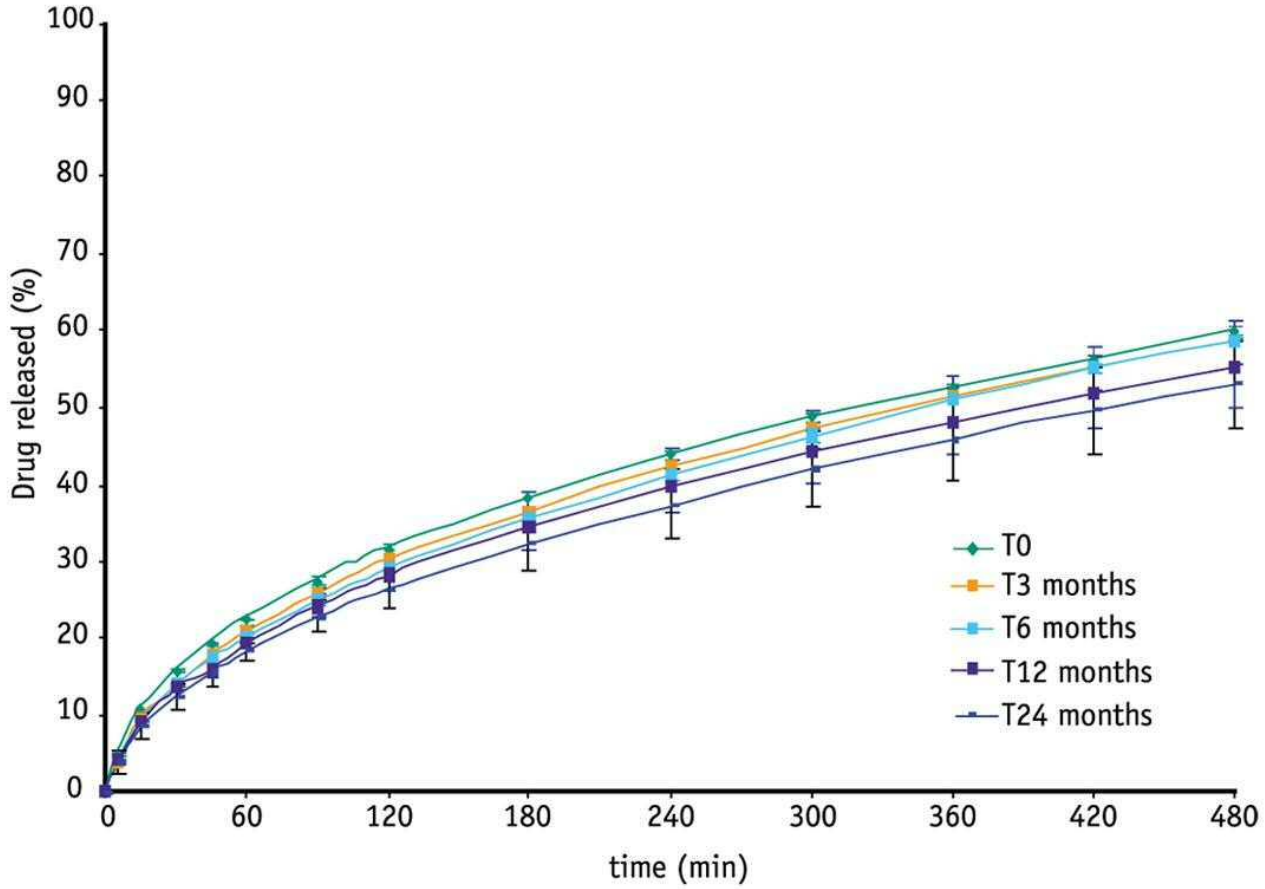
CASE STUDY # 1: SR THEOPHYLLINE TABLET

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



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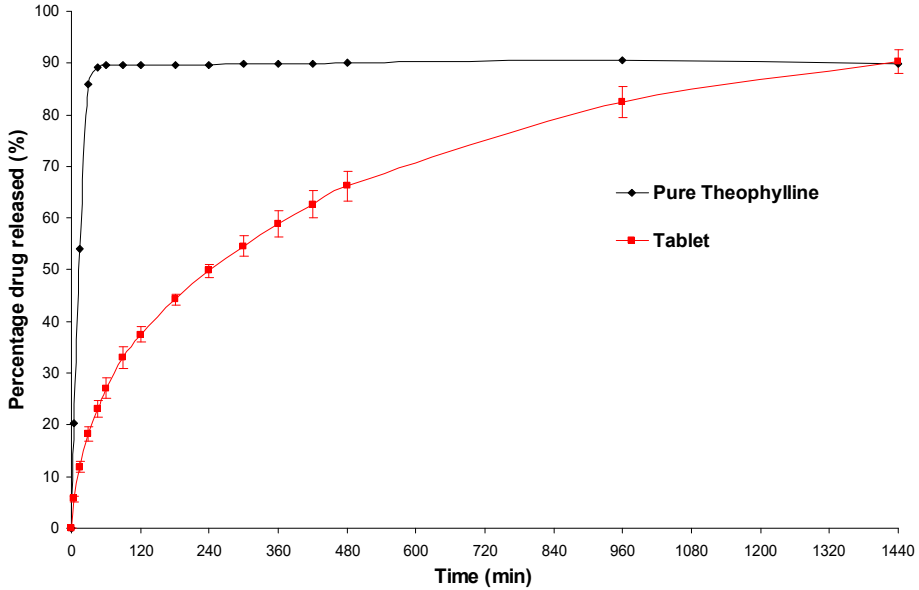

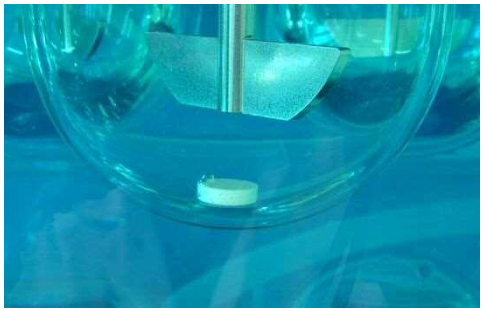

Tablet at t_o

Tablet after 24h

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LIPID MATRIX SR TABLET COMPOSITION

DRUG	Active ingredient
MATRIX FORMER	***Compritol 888 ATO***
DILUENT (co-excipients)	Tablet size, flow, compression *(lactose, MCC, DCPA…)*
LUBRICANT (0.5 – 3%)	Glidant, anti-adhesion, anti-friction *(**Compritol 888 ATO**, talc, Mg stearate...)*

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MAIN CONSIDERATIONS

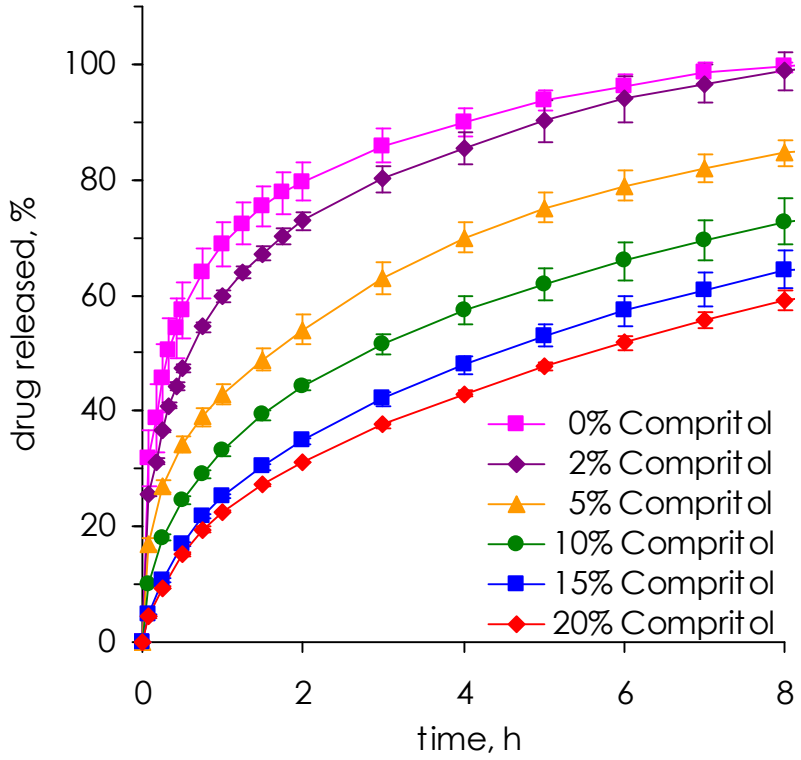
Several **parameters** impacting dissolution/release profile:

- 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*)

IMPACT OF COMPRITOL AMOUNT

Theophylline release of matrix tablets prepared by direct compression.

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



Ingredient	0% C888 % w/w	⇒	20% C888 % w/w
Theophylline	16.7		16.7
Compritol 888 ATO	0		20
DCPA	52.9		39.5
Lactose	26.4		19.8
Mg Al metasilicate	3		3
Mg Stearate	1		1

INCREASE Compritol content

DECREASE drug release

= easy to modulate

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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

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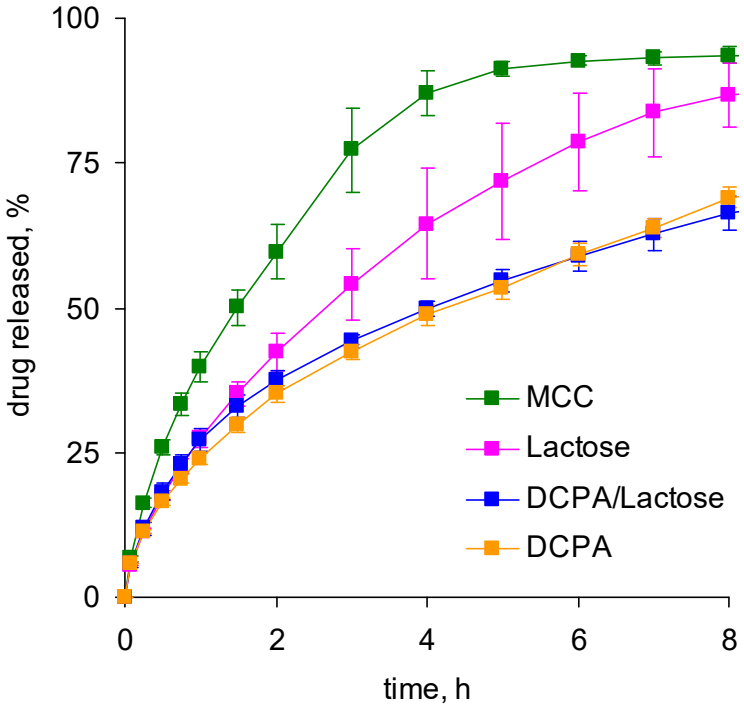
IMPACT OF DILUENTS

Theophylline release of matrix tablets (600mg) prepared by direct compression.

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



Ingredient	% w/w			
Theophylline	16.7	16.7	16.7	16.7
Compritol 888 ATO	15	15	15	15
DCPA	42.9	64.3		
Lactose	21.4		64.3	
MCC PH101				64.3
Neusilin	3	3	3	3
Mg Stearate	1	1	1	1

The nature (and the amount) of diluent plays an important role in the modulation of release rate.

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IMPACT OF COMPRESSION FORCES

Ingredients	%
Theophylline	20
C888 ATO	**15**
Fujicalin SG	32.25
Tablettose 80	32.25
Mg stearate	0.5

Run #	Compression force (kN)	Pre-compression force (kN)	Compression speed (rpm)	Feed rate
Run 1	5.0	1.0	30.0	6.0
Run 4	25.0	1.0	30.0	6.0
Run 5	15.0	1.0	30.0	6.0

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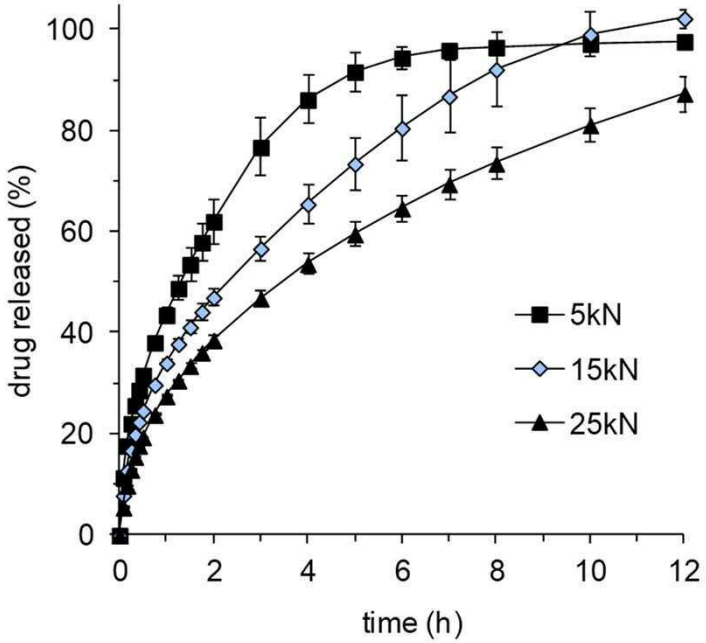
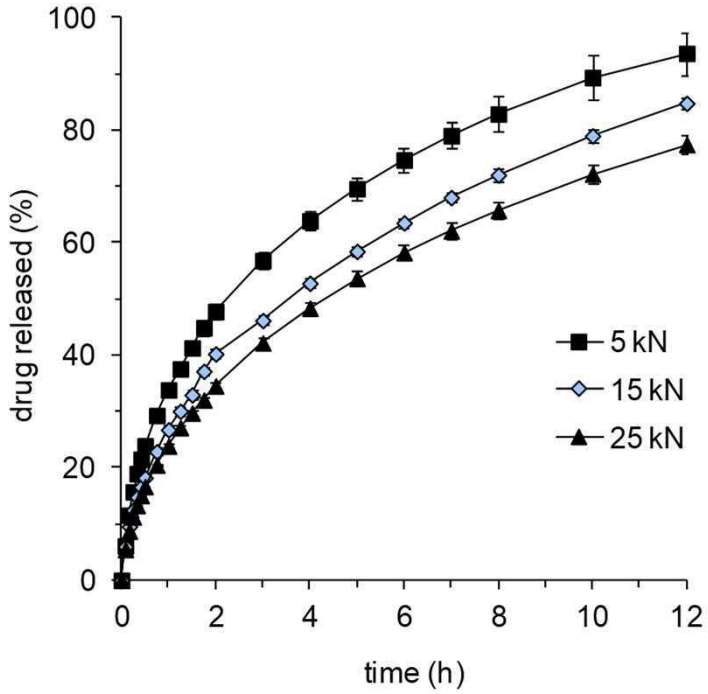
IMPACT OF COMPRESSION FORCES

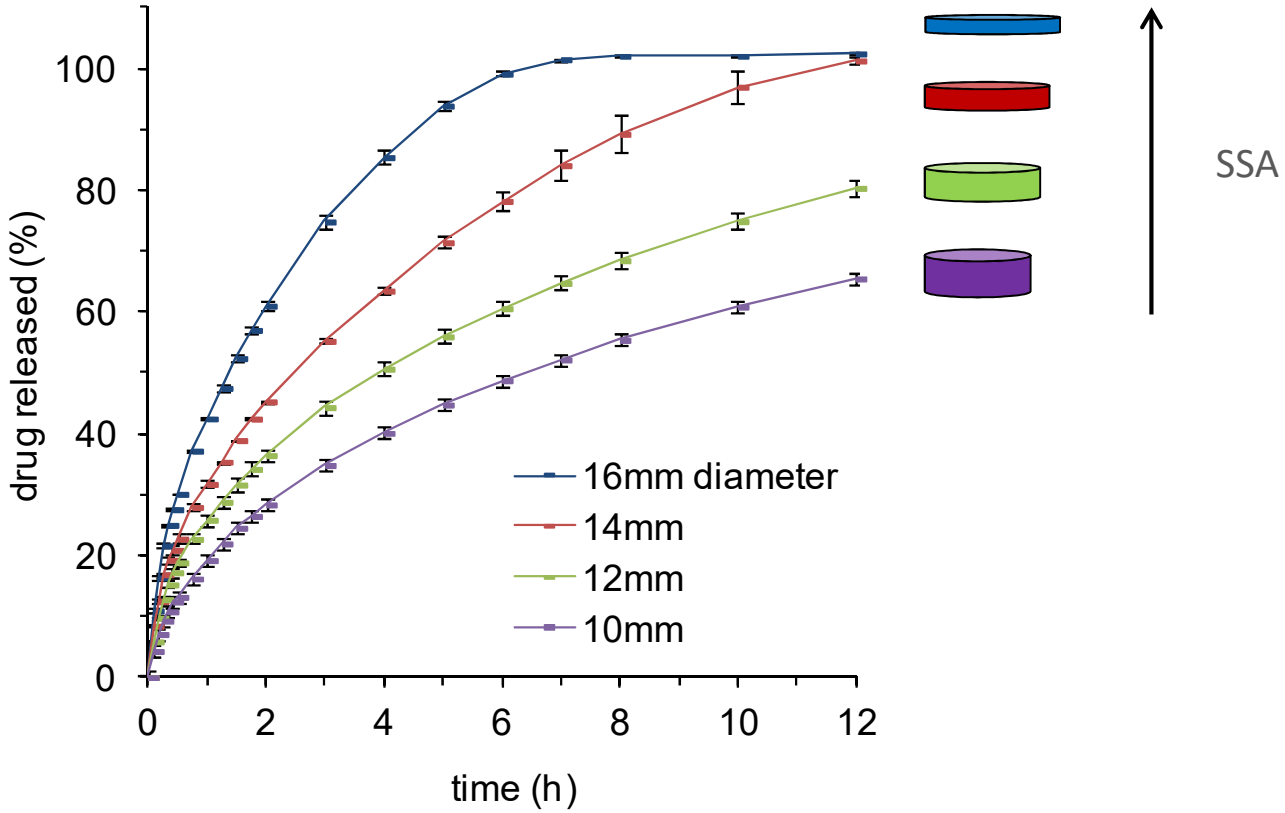


14mm tablets



12mm tablets

IMPACT OF TABLET SIZE



The tablet dimension can be an appropriate tool to adjust drug release kinetics

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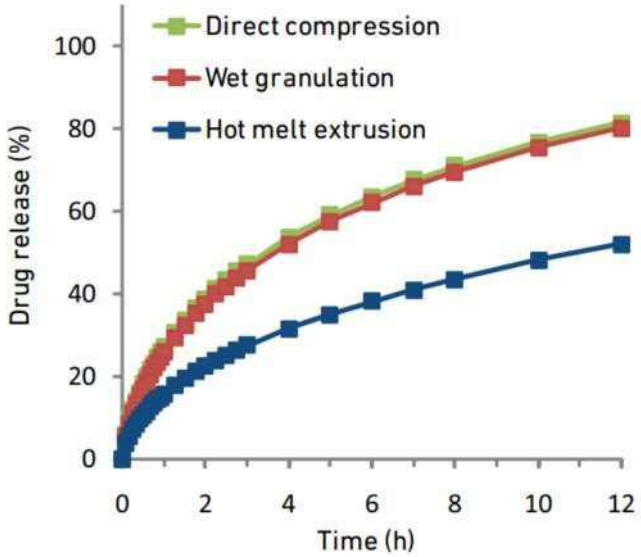
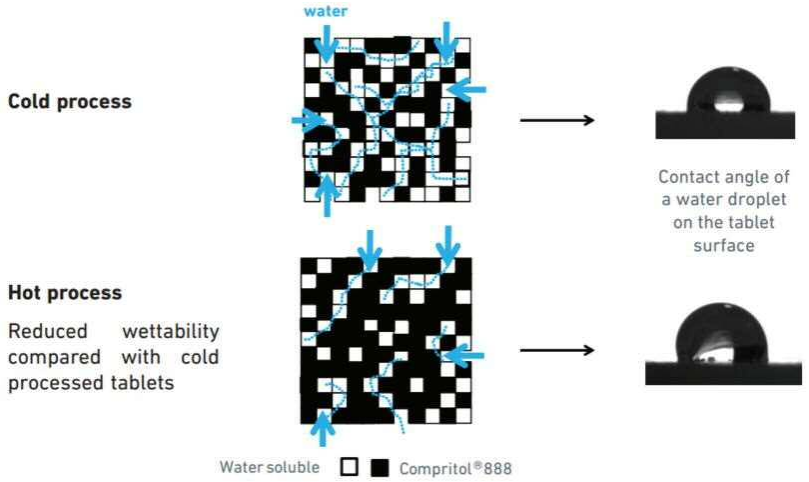
IMPACT OF PROCESSING ROUTE

a) Niacin

Ingredients	Quantity (%)
Niacin	50
Compritol® 888 ATO	30
Povidone	5
Lactose	14.5
Mg stearate	0.5
Tablet weight	1000 mg





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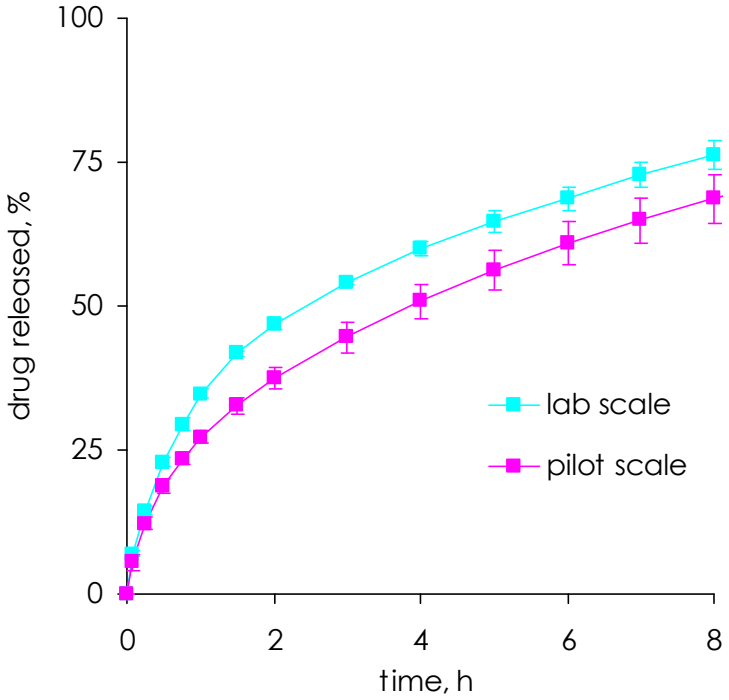
TRANSFERABILITY: SCALE-UP

excenter vs rotary press

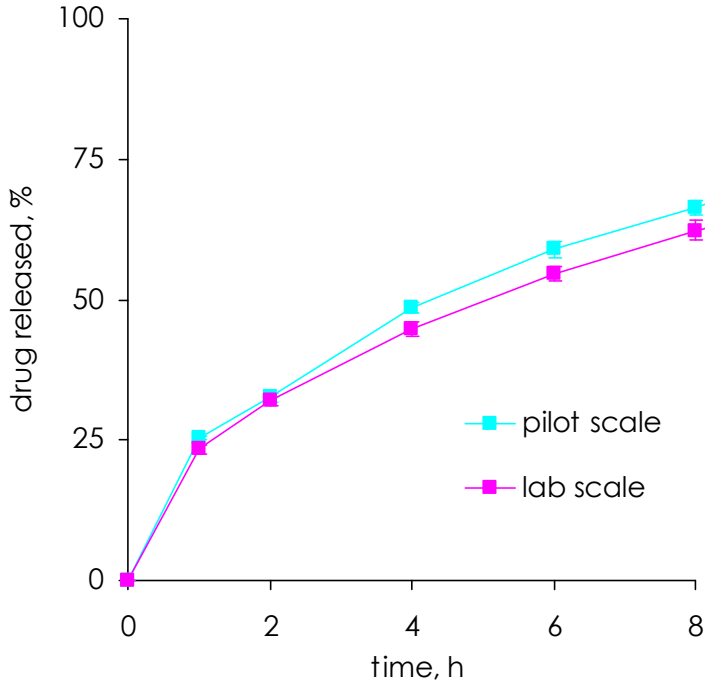
direct compression



Theophylline

small vs high quantity

solid dispersion



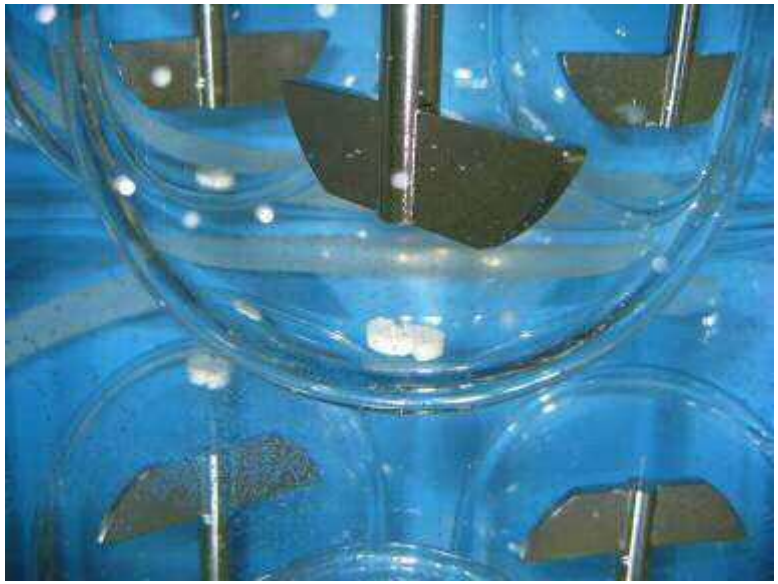
Metoprolol succinate

GATTEFOSSÉ

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.

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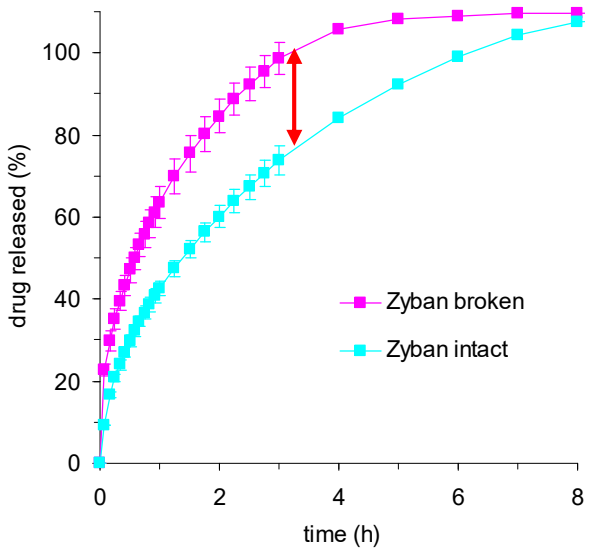
Zyban® is registered trademark of GlaxoSmithKline Ltd.

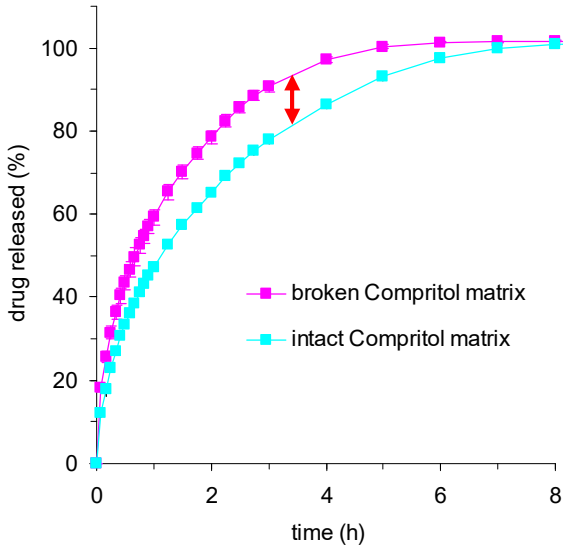
MIS-HANDLING: BUPROPION HCL

Bupropion HCl case study



Zyban® is registered trademark of GlaxoSmithKline Ltd.

Ingredient	DC % w/w
Bupropion HCl	33.3
Compritol 888 ATO	30.3
Cystein HCl	2
DCPA	20.9
Lactose	10.5
Compritol 888 ATO	3
Total weight	450mg



Compritol matrix = SR unaffected

no accidental dose dumping if tablet is broken

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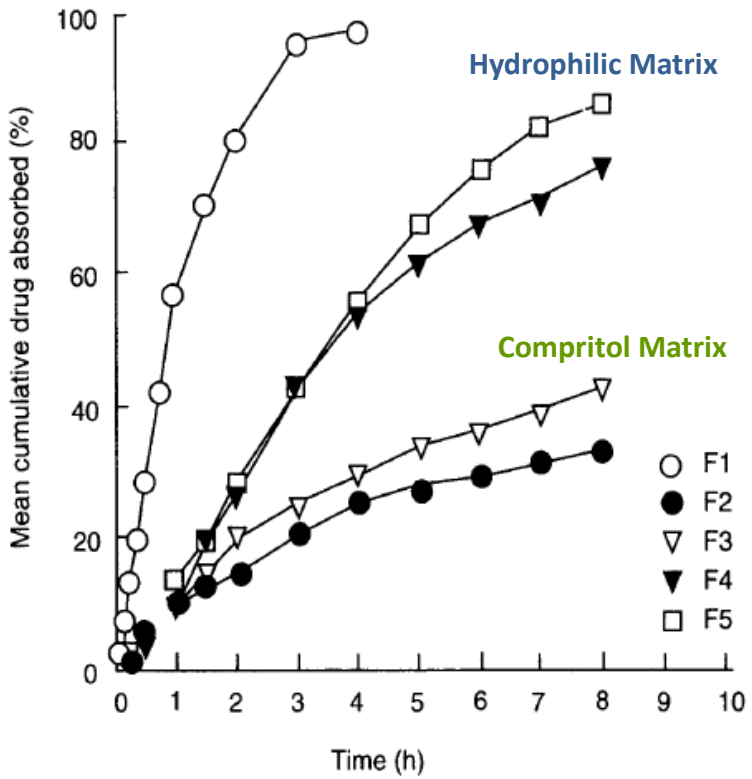
IN-VIVO EFFICACY - THEOPHYLLINE



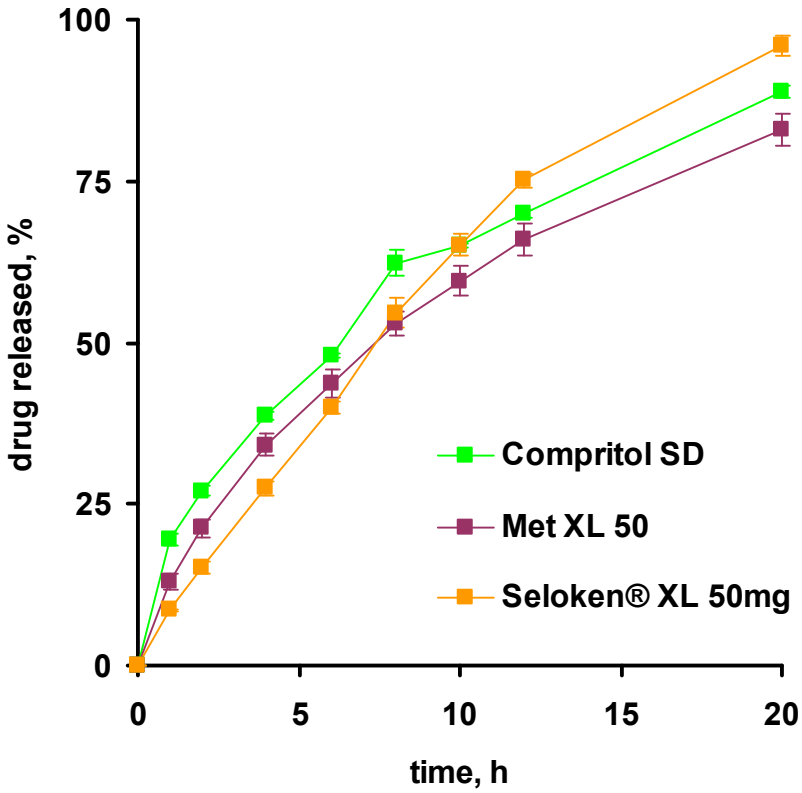
Mean cumulative theophylline absorbed in 8 beagle dogs

Ingredients %w/w	F1	F2	F3	F4	F5
Theophylline	50	**50**	**50**	50	50
Compritol 888		**30**	**30**		
Carbomer				30	
HPMC					30
Spray-dried lactose		**20**		20	
DCPA	50		**20**		
MCC					20
Totals	100	100	100	100	100

Tablet weight 200 mg made by direct compression

G.El-Sayed et al. STP Pharma Sciences 6(6):398-402 (1996)

MARKET REFERENCE COMPARISON



In vitro metoprolol succinate release from lipid matrix closely matches market references

Tablet Ingredients	% w/w	mg
Metoprolol succinate	28.55	50
Compritol 888 ATO	57.11	100
MCC PH-101	11.42	20
Magnesium stearate	1.94	3.4
Aerosil	0.97	1.7
Total weight (mg)	100	175.1

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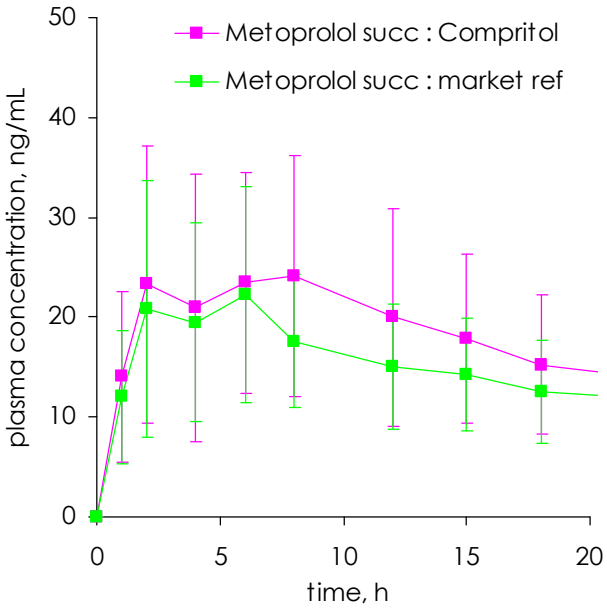
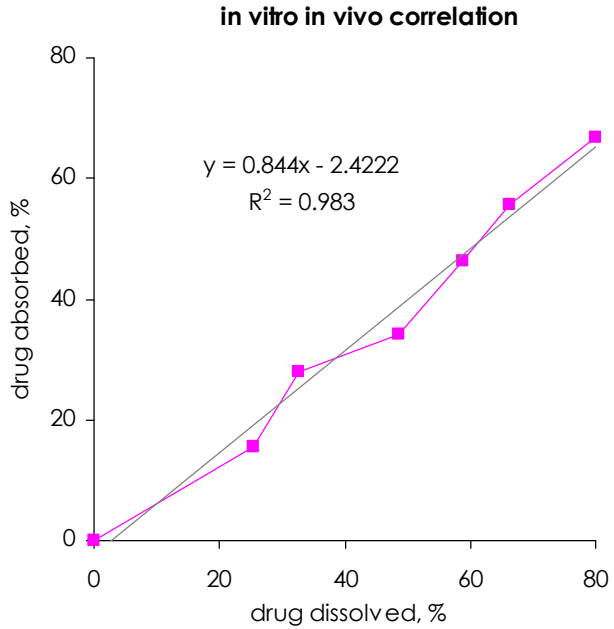
IVIVC – METOPROLOL SUCCINATE

In vivo study in 12 healthy men





1- The plasma concentration time profile of Compritol tablet and MetXL50 is comparable

2- The R^2 values in the IVIVC indicates excellent correlation

Poster : Controlled Release Society Annual Meeting 2011: ***Compritol® 888ATO a release modifier for sustained release of highly water soluble agent: Formulation, Evaluation and IVIVC study. M. S. Nagarsenker et al.***

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PRESENTATION CONTENTS

- 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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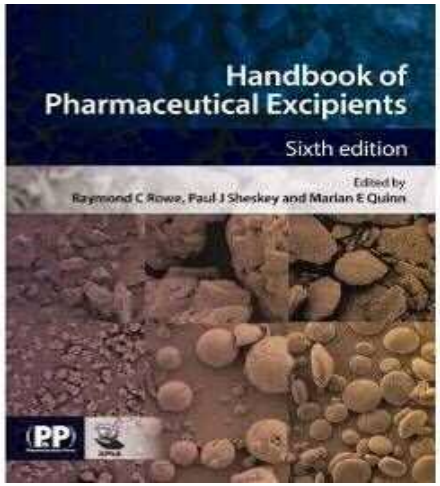
COMPRITOL 888 ATO

Performance & flexibility

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

Pharmacopoeia, GRAS

Well characterized



Global regulatory acceptability

Patent opportunities

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GLYCERYL BEHENATE IN APPROVED DOSAGE FORMS

Active ingredient	Matrix / drug delivery technology system
Ropinirole	Multilayed / controlled release DDT
Prednisone	Multi-layer / core timed release DDT
Tilidine	Matrix tablet
Theophylline	Matrix tablet
Paroxetine	Matrix tablet
Metformin HCL	Matrix tablet
Nisoldipine	Multilayed / controlled release DDT
Zileuton	Multilayed / controlled release DDT
Valproic acid	Microgranules
Nicotinic acid	Matrix tablet
Azithromicine	Coated microgranules / suspension
Ibuprofen	Matrix tablet
Guanfacine HCl	Matrix tablet

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CASE STUDIES AVAILABLE

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

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LIPID MATRIX: A SMART STRATEGY

Thank you!

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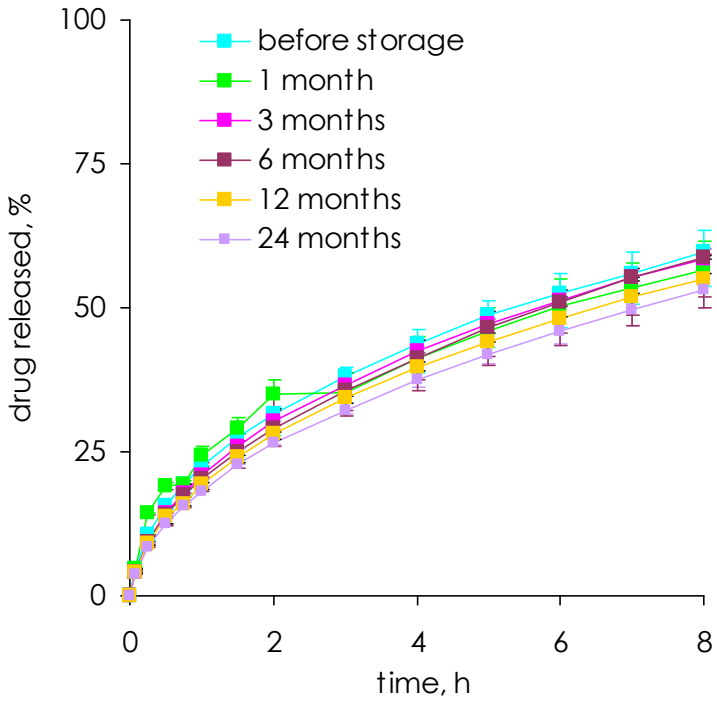
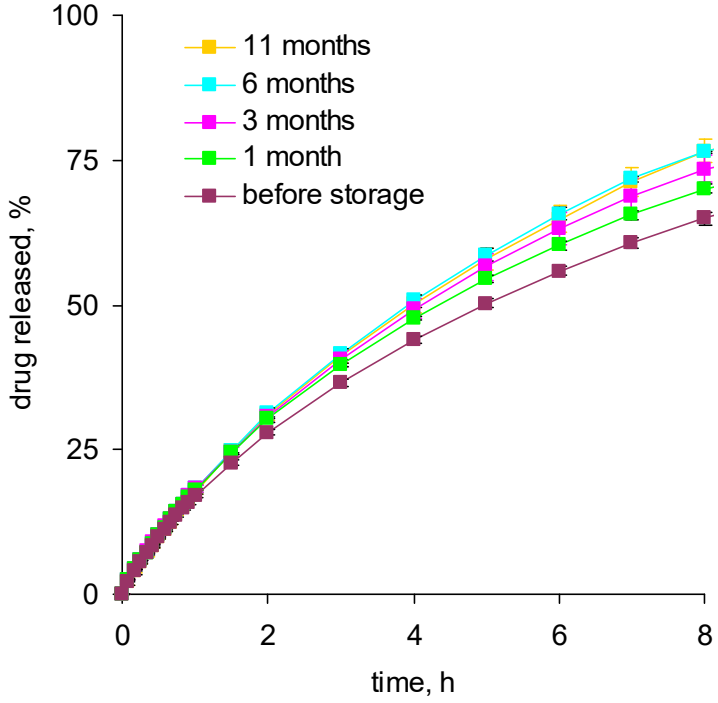
APPENDIX

STORAGE STABILITY

Theophylline - direct compression



Diclofenac Na – solid dispersion



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

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