GATTEFOSSÉ

Developing sustained release tablets with Compritol® 888 ATO

Formulation guideline

People make our name

FOREWORD

Gattefossé Application Laboratories - in France, China and India - undertake detailed studies to characterize the performance of Gattefossé lipid excipients with model active pharmaceutical ingredients (API) in formulations and numerous different processes. The resulting knowledge provides customers with practical solutions, formulation guidelines as well as trustworthy ideas for innovative drug development.

This formulation guideline aims to provide formulation scientists with comprehensive and clear information on the physico-chemical and biopharmaceutical properties of **Compritol® 888 ATO (glycerol dibehenate)** and how this highly versatile excipient can be used to **create effective sustained release (SR) matrices**. A detailed description of Compritol® 888 ATO characteristics and specifications is provided as well as tips for tablet formulation and manufacturing processes. Case studies illustrate the potential of Compritol® 888 ATO in SR formulation. Practical solutions to common problems encountered in SR development are also included.

We welcome your comments and suggestions about this guideline at: infopharma@gattefosse.com

ABBREVIATIONS:

API: Active Pharmaceutical Ingredient; **CF:** Compaction Force; **ChP:** Chinese Pharmacopoeia; **CPP:** Critical Process Parameter; **CS:** Compaction Speed; **DC:** Direct Compression; **DCP:** DiCalcium Phosphate; **DCPA:** DiCalcium Phosphate Anhydrous; **DMF:** Drug Master File; **EC:** Ethyl Cellulose; **EP:** European Pharmacopoeia; **FAO/WHO:** Food and Agriculture Organisation/World Health Organization; **FCC:** Food Chemical Codex; **FDA:** Food and Drug Administration; **GRAS:** Generally Recognized as Safe; **HME:** Hot Melt Extrusion; **HPC:** HydroxyPropyl Cellulose; **HPMC:** HydroxyPropylMethyl Cellulose; **IID:** Inactive Ingredient Database; **IVIVC:** In Vitro In Vivo Correlation; **JSFA:** Japanese Standards for Food Additives; **MCC:** Micro Crystalline Cellulose; **MFT:** Minimum Film forming Temperature; **MP:** Melting Point; **PCF:** Pre-Compaction Force; **PEO:** PolyEthylene Oxide; **PVP:** Poly Vinyl Pyrrolidone; **SR:** Sustained Release; **Tg:** Glass Transition Temperature; **USP/NF:** US Pharmacopoeia/National Formulary; **WG:** Wet Granulation

Contents

1. Compritol 888 ATO in SR matrices at a glance

Composition

A well-defined excipient constituted of mono, di and triglycerides of behenic acid (C_{22}), the di-ester fraction being predominant (40 – 60%)

Regulatory properties

- Glyceryl (di) behenate conforms to EP, USP and ChP
- Food additive status FCC/GRAS/JSFA
- USA FDA IID oral reference: 2 g/unit dose (as a powder for suspension)
- USA FDA Type IV DMF
- Listed in Handbook of Pharmaceutical Excipients

Physical properties

Form	Powder
Particle size distribution (Granulometry)	mean particle size of 50 µm narrow size distribution
Drop Point (°C)	Mean: 72.4 (± 0.4) (n= 233)
Crystallization temperature (°C)	71.0
Viscosity (mPa.s)	25 (± 1)(80°C)(n=3) thermorheometer type rotor/stator

Solubility

Dispersion in water	Insoluble (ambient T°)
Solubility in ethanol 96°	Insoluble (ambient T°)
Solubility in chloroform, methylene chloride	Soluble (ambient T°)
Solubility in n-hexane	Insoluble (ambient T°)

Common uses

Sustained/controlled release matrix former for tablet/granules, lubricant, taste-masking and API protecting agent, nanoparticle synthesis

Common processes

Wet granulation, direct compression, hot melt coating and extrusion

Precedence of use in controlled release tablet

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

Non-exhaustive list

Precedence of use in special indications

Guanfacine Hydrochloride	**Attention Deficit Hyperactivity Disorder in children**
Azithromycin	**Antibacterial - suspension for use in children**

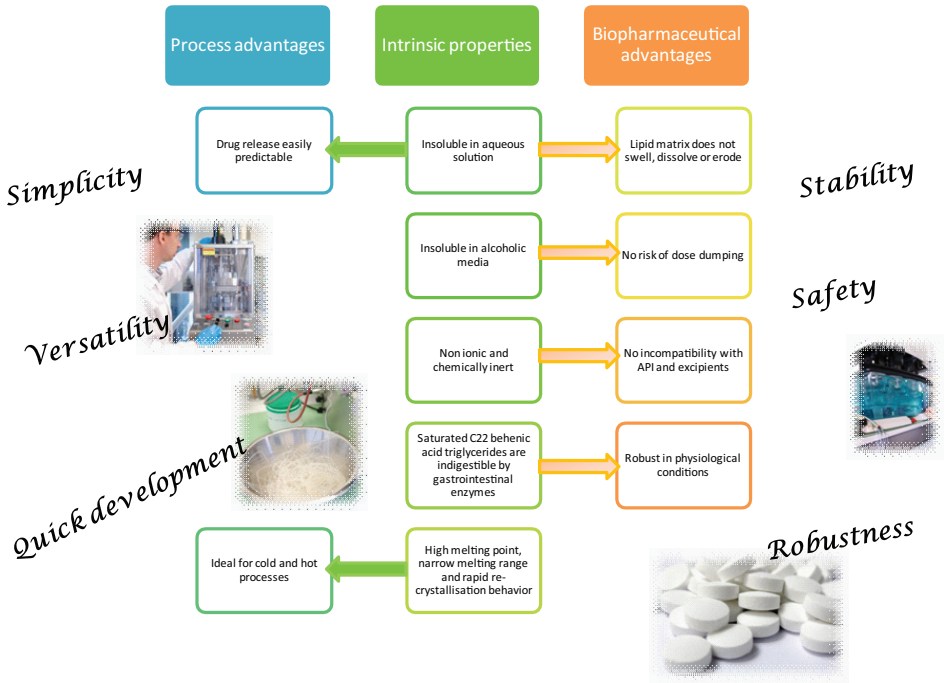
QbD dossier is available on request

2. Introduction to Compritol® 888 ATO in sustained release matrices

2.1 Main features of Compritol® 888 ATO in SR matrices

Compritol® 888 ATO combines several advantages when used as a sustained release matrix agent. These will be explained and illustrated throughout this Guideline.

- Drug release from a Compritol® 888 ATO matrix is diffusion controlled and not driven by swelling and erosion. This facilitates **simple product design, including straightforward modulation of drug release and high reproducibility.**
- A Compritol® 888 ATO matrix is not sensitive to physiological variations such as pH, digestion or alcohol. It makes biopharmaceutically **robust tablets.**
- **Versatile use of Compritol® 888 ATO in many processing techniques** favors product optimization and provides scope for innovation in solid oral dosage form development.



2.2 Main differences between Compritol® 888 ATO and polymers

Pharmaceutical polymers, for example hydroxypropyl methylcellulose, hydroxypropyl cellulose, ethylcellulose and polyethylene oxide, are commonly used in SR matrix tablets. Compritol® 888 ATO is very different to these polymers in terms of physicochemical properties and drug release mechanism as illustrated in Table 2-1 and in Figure 2-1.

Table 2-1 Compared physicochemical properties and drug release mechanism of Compritol® 888 ATO and pharmaceutical polymers

Criteria	Compritol® 888 ATO	Polymer
Origin	**Vegetable**	Natural, (semi-) synthetic
Molecular weight	**Low**	Medium to high
Structure	**Crystalline**	(Semi-) amorphous
Thermal behavior	**Melting point**	Glass transition temperature Minimum film-formation temperature melting point
Melting point	**Low (70°C)**	**High (>100°C)**
Solubility in water	**No**	Polymer dependent
Solubility in organic solvents	**No**	Yes, for most polymers
Digestibility	**No**	Polymer dependent
pH-dependent	**No**	Polymer dependent
Chemical reactivity	**No**	Polymer dependent
Drug release mechanism	**Diffusion**	**Swelling and/or erosion and/or diffusion (polymer dependent)**

Compritol® 888 ATO is a crystalline material whereas polymers are amorphous. As such the thermal behavior of Compritol® 888 ATO is different, illustrated by a sharp melting point, around 70 °C, and a full recrystallization (at 68 °C). It can therefore be used in liquid form in hot processes, such as extrusion, with a process temperature below 80 °C. In contrast, polymers have a glass transition temperature (Tg) above 100 °C upon which the material becomes soft but not liquid. When used in extrusion, polymers require a process temperature about 20 °C above Tg, i.e. >120 °C.

Drug release mechanism is one of the major difference between Compritol® 888 ATO and polymers when used as SR agents.

High viscosity HPMC is a **water-soluble** excipient that is widely used in SR tablets. On contact with the aqueous medium, HPMC jellifies forming a hydrophilic barrier which prevents immediate drug release. Drug diffuses out slowly from the jellified matrix which dissolves and erodes over time. The matrix geometry therefore constantly changes, potentially providing zero order release kinetics (Figure 2-1 top).

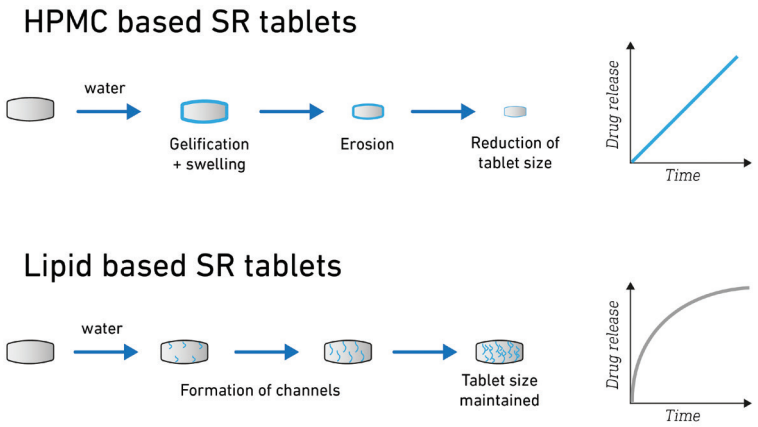


Figure 2-1 Compared physicochemical properties and drug release mechanism of Compritol® 888 ATO and pharmaceutical polymers

In contrast, Compritol® 888 ATO is a **water-insoluble** excipient which does not swell or erode in contact with the aqueous medium (Figure 2-2). When it is used as an SR agent in tablet it forms an inert matrix through which the drug diffuses out slowly. The matrix geometry/tablet size does not change throughout dissolution. Therefore, it is suggested that drug release is governed by pure diffusion and the release kinetic is principally first order (Rosiaux et al, 2014d) (Figure 2-1 bottom).

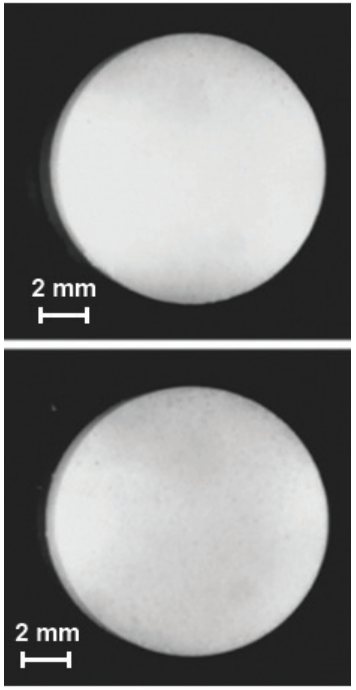


Figure 2-2 Aspect of tablets containing Compritol® 888 ATO before (top) and after (bottom) drug release for 24 h

Drug release from Compritol® 888 ATO matrix is driven by a pure diffusion mechanism. This makes the prediction of drug release rate possible by a simplified calculation approach as described by *Rosiaux et al, 2014d*.

2.3 Compritol® 888 ATO provides process flexibility

Due to its specific thermal behavior, Compritol® 888 ATO can be used in both cold and hot processes as listed in Table 2-2.

As such it provides scope for innovation in oral solid dosage form development such as the reformulation of drugs into different dosage forms such as tablets, mini-tablets, granules or capsules.

Table 2-2 Possible processing techniques with Compritol® 888 ATO

Process	Equipment
Direct compression	Tablet machine
Dry granulation	Roller compacter
Wet granulation	High-shear mixer / fluid bed
Melt granulation	Jacketed high shear mixer, fluid bed (jacketed tubing*), twin screw extruder
Melt & Mix**	High shear mixer / jacketed high shear mixer
Molding/casting	Hot liquid capsule filling machine
Spray cooling/congealing	Spray congealer
Prilling	Prilling tower
Melt extrusion	Twin screw extruder
Melt coating	Fluid bed (jacketed tubing)
Pressure homogenization	High pressure homogenizer
Emulsion congealing	Spray congealer

** Jacketing is not required if the lipid is pre-blended with the drug and the blend heated in the chamber*

*** Melt & Mix = Drug dispersed in melted lipid by simple mixing*

3. Compritol® 888 ATO properties

3.1 Product description

Compritol® 888 ATO is a fine white powder, insoluble in water and organic solvents. It has no odor and no taste. It is used as lubricant, coating agent for the protection of sensitive drugs, in taste masking and as a matrix former in sustained release.

3.2 Composition

Compritol® 888 ATO is an ester of mono-, di- and triglycerides, the die-ester fraction is predominant (40 – 60%). It is composed of glycerol and fatty acids of behenic acid (C_{22}) from vegetable origin (Figure 3-1).

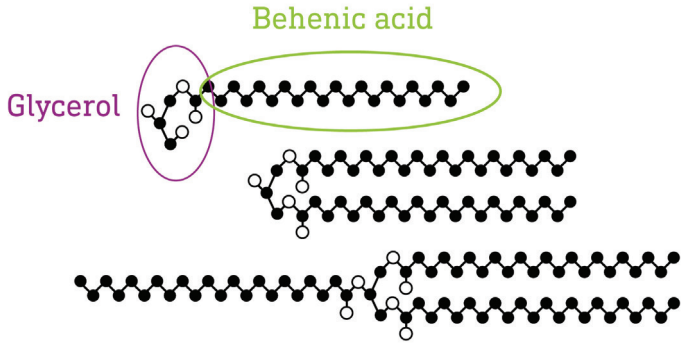


Figure 3-1 Chemical composition of Compritol® 888 ATO

Gattefossé production process ensures Compritol® 888 ATO batches have high reproducibility and constant composition.

A complete analytical file is available upon request to support your Quality by Design needs.

3.3 Physicochemical properties

Particle size

Compritol® 888 ATO particles have a spherical shape (Figure 3-2), a mean particle size of 50 µm and a narrow size distribution.

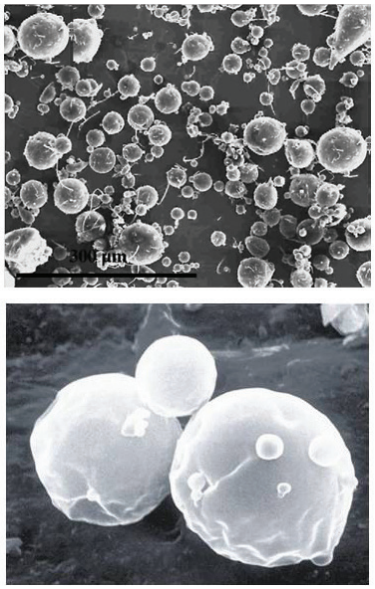


Figure 3-2 Compritol® 888 ATO spherical particle shape of 50 µm mean diameter

Thermal behavior (DSC and Thermorheogram)

Using Differential Scanning Calorimetry, the melting onset is 68 °C with a melting peak at 71 °C. It crystallizes instantly at 68 °C (Figure 3-3). This quick change of state, from solid to liquid, is also observed through viscosity measurements (Figure 3-4).

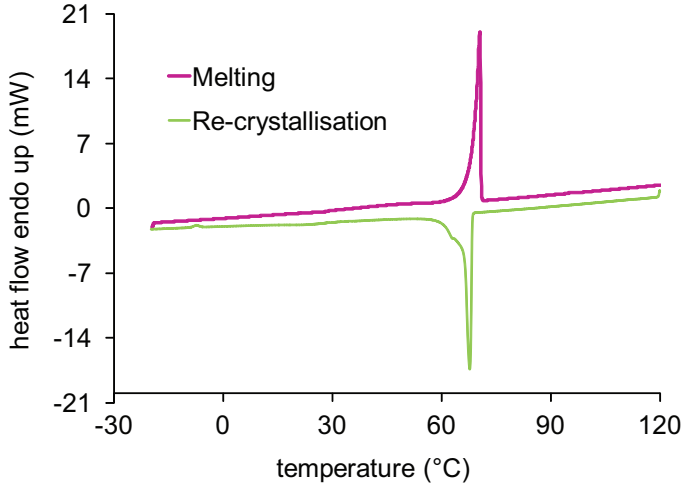


Figure 3-3 Compritol® 888 ATO melt and crystallization thermogram (DSC method)

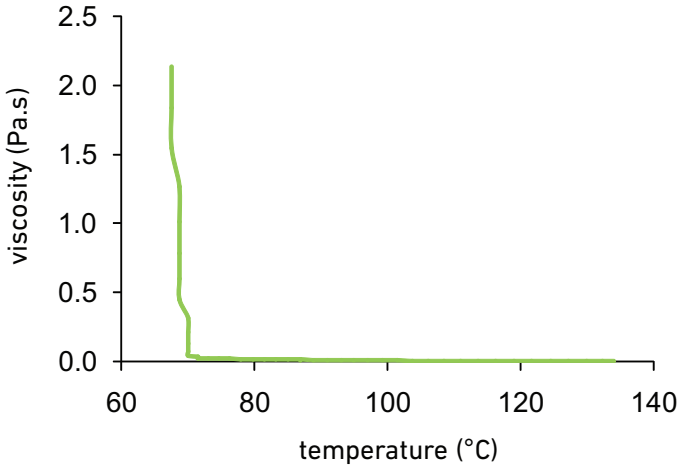


Figure 3-4 Thermorheogram of Compritol® 888 ATO

Water uptake (hydroscopicity)

Compritol® 888 ATO is completely hydrophobic due to the length of its C_{22} fatty acid chains. The powder does not become significantly moist (<3% water uptake), even when exposed to 100% relative humidity (Figure 3-5).

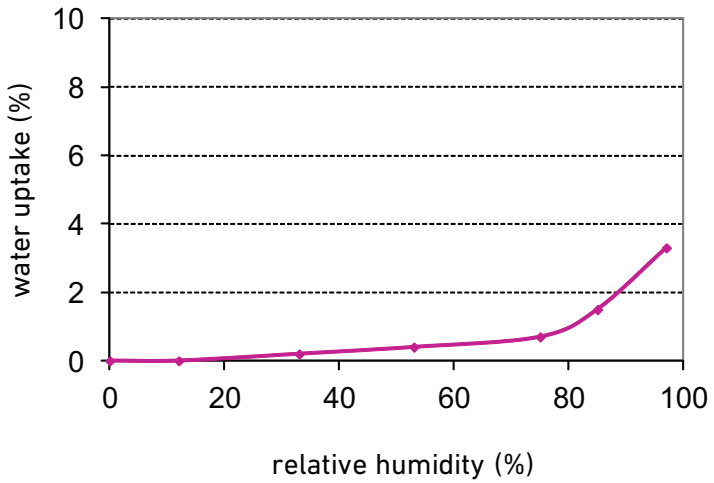


Figure 3-5 Chemical composition of Compritol® 888 ATO

Stability

Compritol® 888 ATO is stable for three years in sealed original packaging - stored below 35 °C (Figure 3-6). The crystalline structure as well as particle size and specifications remain unaltered.

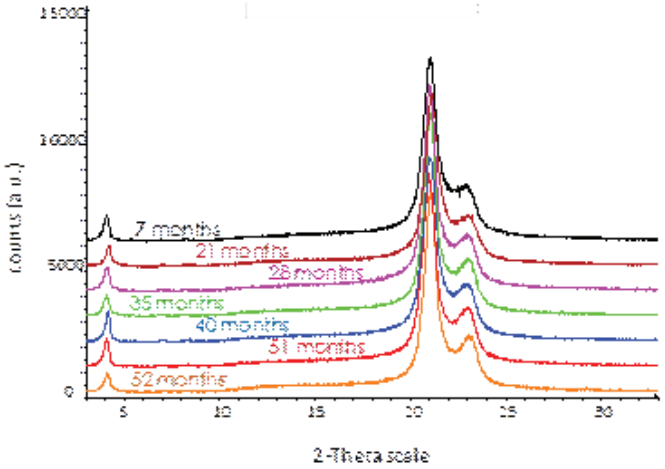


Figure 3-6 Diffraction pattern of Compritol® 888 ATO in long-term stability at ambient storage temperature

The chemical stability of Compritol® 888 ATO under process conditions has been assessed by an extrusion process at 180 °C (Rosiaux et al, 2014a). At this high temperature no chemical change or degradation was observed.

3.4 Regulatory status

Compritol® 888 ATO has a long history of use as a pharmaceutical ingredient and is globally approved and listed in several monographs (Table 3-1). Compritol® 888 has a Type IV-Excipient Drug Master File (DMF) in the US. The to-date listed **USA FDA IID value is 2 g/unit dose (as a powder for suspension).**

Table 3-1 Compritol® 888 ATO Pharmacopoeia conformity

Pharmacopoeia	Monograph
EP	Glycerol dibehenate
USP/NF	Glyceryl dibehenate
Ch.P.	Glyceryl behenate

Glycerides have been used worldwide for many years as additives in food, nutraceutical products and dietary supplements and Compritol® 888 ATO is listed in several food additive references (Table 3-2).

Table 3-2 Compritol® 888 ATO food additives conformity

Food additive reference	Registration number
FAO/WHO Expert Committee on Food Additives	INS471 Mono- and Diglycerides
FCC (Food Chemical Codex)	Mono- and Diglycerides
GRAS (Generally Recognized As Safe according to 21 CFR	21 CFR §184.1505 Mono- and Diglycerides
JSFA (Japanese Standards of Food Additives)	Glycerol esters of fatty acids

Note that a specific grade Compritol® E ATO is also available with European food additives conformity

4. Developing sustained release formulations with Compritol® 888 ATO

4.1 Defining key formulation objectives

Before starting any controlled release formulation development, the key **objectives** must be clearly defined and the **API properties** well characterized. Table 4-1 lists the most important objectives to consider. Data including drug solubility in aqueous media, dose and the target *in-vitro* release profile (rate and duration) will define the release retarding properties that the matrix should be designed to provide.

Table 4-1 Pre-requisites before starting SR formulation development

Key objectives	API properties
Desired drug dose (in mg API/unit)	Water solubility
Drug release rate (in % vs time in hours)	Melting point
Final dosage form (tablet, granule, ...)	Particle size and shape
Preferred process	Flow and compactability
In-house processing facilities	Heat sensitivity

4.2 How to start with Compritol® 888 ATO

Extensive formulation studies undertaken in Gattefossé laboratories have enabled the elucidation of several useful starting points in matrix tablet development Designing a Compritol® 888 formulation for matrix tablet is relatively straightforward because drug release is controlled by diffusion. When Compritol 888 ATO is the only release retarding agent used then the API aqueous solubility and nature of the diluent will impact on matrix structure and solubility hence drug release properties. API aqueous solubility gives an indication of how release retarding the matrix needs to be, ie. what concentration of Compritol 888 ATO will be required to provide slow drug release.

Table 4-2 gives simple guidelines for starting points in SR tablet development by direct compression based on API solubility in water.

Table 4-2 Straightforward guideline for starting SR formulation with Compritol® 888 ATO

Drug solubility in release medium	< 1 mg/mL	1 - 50 mg/mL	> 50 mg/mL
Example	Nifedipine	Theophylline	Metformin HCl
	Ibuprofen	Niacin	Bupropion HCl
	Ketoprofen	Diclofenac Na	Metoprolol succinate
Compritol® 888 ATO concentration	< 15%	10 - 25%	> 20%
Diluents type	Water soluble (+ solubilizer)	Soluble/insoluble	Water insoluble

Poorly soluble drugs (<1 mg/mL)

Require a low concentration of Compritol® 888 ATO in tablets made by direct compression.

Compritol 888 ATO is insoluble therefore a wetting agent may be required to enhance drug solubility in the aqueous media - depending on the dose.

A water-soluble diluent can be used to adjust drug release to obtain the target profile.

Moderate (1-50 mg/mL) / freely soluble drugs (>50 mg/mL)

Generally require higher concentrations of Compritol® 888 ATO and a wetting agent is unlikely to be necessary.

The addition of the right water-insoluble / water-soluble diluents enables fine-tuning of the drug release kinetic.

4.3 How to adjust the drug release profile

If the target drug release profile is difficult to achieve different solutions can be proposed based on formulation and/or process modifications, these are described below.

1. Adjust Compritol® 888 ATO concentration

Reproducible SR matrix systems rely on the use of a minimum concentration of Compritol® 888 ATO to create an infinite matrix network throughout the dosage form. This minimum Compritol® 888 ATO concentration is known as the 'percolation threshold' and should be considered when designing a lipid matrix tablet (Rosiaux et al, 2013). The simplest way to modulate drug release is by changing the concentration of Compritol 888 ATO in the formulation. **Increasing the concentration of Compritol® 888 ATO will retard drug release and decreasing Compritol® concentration will accelerate drug release** (Figure 4-1).

Theophylline water solubility is 10 mg/mL. Tablets made with an increasing amount of Compritol® 888 ATO, from 5% to 40%, were evaluated. Figure 4-1a clearly shows that increasing Compritol® 888 ATO slows down drug release. In this case, the minimum amount of Compritol® 888 ATO required to obtain the target sustained-release profile was 20%.

Metformin HCl has higher aqueous solubility (330 mg/mL) and therefore requires a higher concentration of Compritol (45%) to deliver the target sustained-release profile (Figure 4-1b).

The minimum Compritol® 888 concentration to provide reproducible prolonged drug release is dependent on drug solubility, dose and the targeted release kinetic.

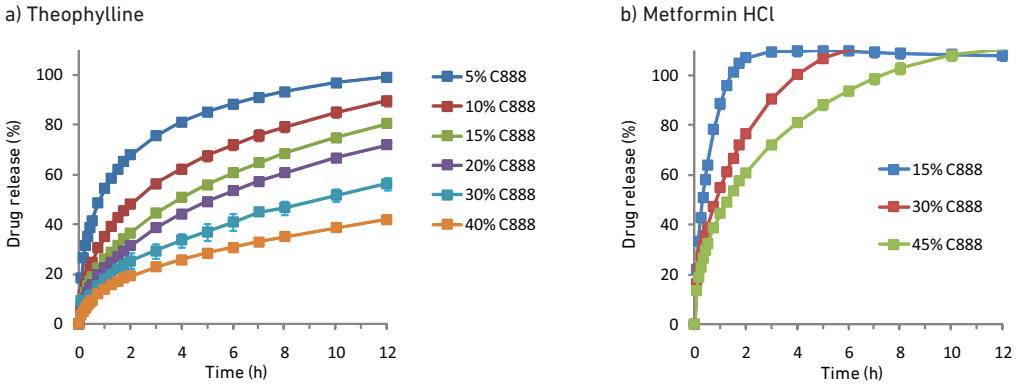


Figure 4-1 Effect of the Compritol® 888 concentration on: a) theophylline release in pH 4.5 and b) metformin release in pH 6.8 at 37 °C from sustained release matrix tablets referring to the respective USP monographs (20% drug, 80% Compritol 888 / diluents, 0.5% magnesium stearate, tablet weight 500 mg, direct compression process)

READ MORE

Percolation threshold of Compritol® 888 in matrix tablets: assessing the minimum concentration to create an infinite lipid network.

AAPS poster
Rosiaux Y. et al, 2013.

2. Adjust the diluent

If Compritol® 888 ATO is the unique **release retarding agent** in the matrix, drug release will be driven by diffusion. As such the solubility of other ingredients - such as diluents - in the formulation will affect the release kinetic. **Therefore the selection of the right diluent is essential to obtain the desired drug release profile.**

A range of diluents with different solubility were screened to evaluate their effect on theophylline release from Compritol 888 ATO SR tablets (Table 4-3):

- Group 1: various grades of insoluble DCP
- Group 2: different grades of practically insoluble celluloses
- Group 3: soluble sugars

Table 4-3 Water solubility of common pharmaceutical diluents

Filler	Market name	Solubility in water at 20°C	Group
Sucrose	CompriO	**1 in 0.5**	3
Lactose	Tablettose 80	**1 in 5.24**	
	Lactopress spray dried	**1 in 6.15**	
	Flowlac 100	**1 in 8.73**	
Lactose/starch (85/15)	StarLac	**Partially soluble**	
Lactose/MCC (75/25)	MicroceLac 100	**Partially soluble**	2
MCC	Vivapur 102	**Pratically insoluble**	
	Avicel PH-101	**Pratically insoluble**	
	Avicel PH-200	**Pratically insoluble**	2'
DCPA	Fujicalin SG	**Pratically insoluble**	1
	Emcompress anhydrous	**Pratically insoluble**	
DCP	Emcompress Premium	Pratically insoluble	

The drug release profiles from tablets made with Compritol 888 ATO (19.5%) and various diluents are shown in Figure 4-2.

Drug release was faster in theophylline tablets containing lactose (group 3) compared to MCC (group 2) and DCP(A) (group 1).

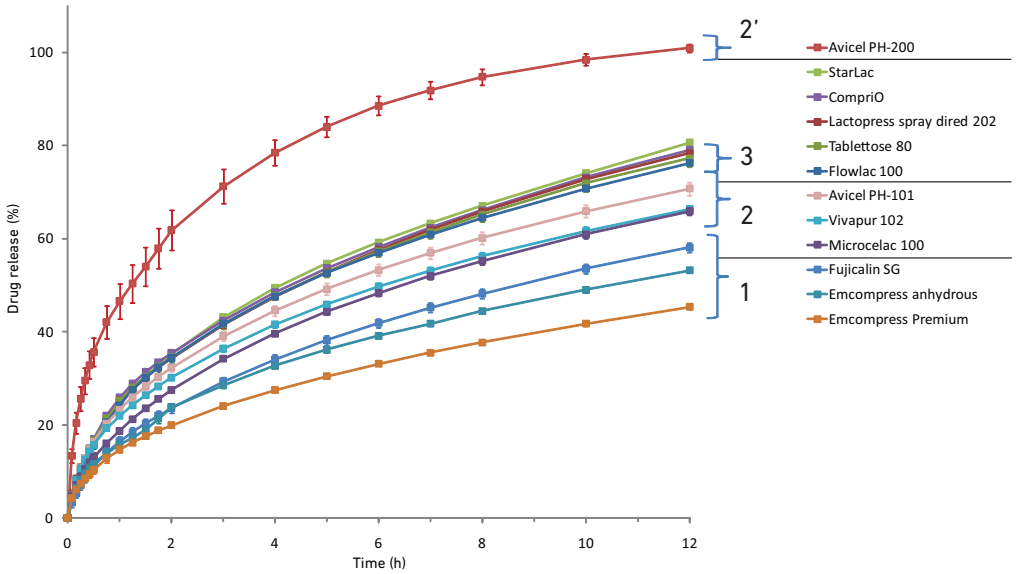


Figure 4-2 Effect of filler solubility on theophylline release from Compritol® 888 ATO matrix tablets (30% drug, 19.5% Compritol 888, 50% diluent, 0.5% magnesium stearate, tablet weight 333.3mg, direct compression process)

The water solubility of the diluent directly impacts the drug release rate.

With MCC (group 2), swelling and disruption of the lipid matrix is observed after water uptake (Figure 4-3) leading to an increase in the surface area to volume ratio for drug diffusion. This results in faster drug release. Interestingly, this effect appears to be more pronounced when using larger, spherical shaped MCC particles with low moisture content: Avicel PH200> Avicel PH101> Microcelac 100> Vivapur.

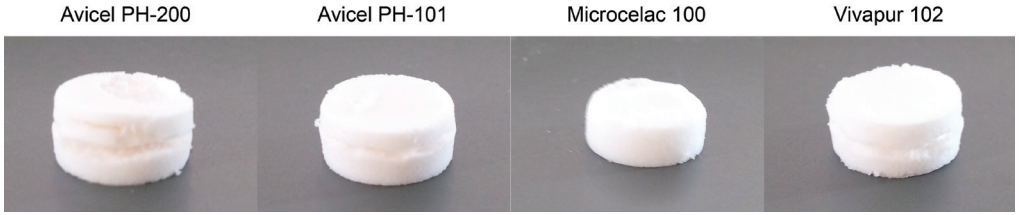


Figure 4-3 Aspect of tablets containing Compritol 888 and different MCC grades after 12h of dissolution in phosphate buffer pH 4.5 (30% drug, 19.5% Compritol 888, 50% diluent, 0.5% magnesium stearate, tablet weight 333.3mg, direct compression process)

MicroceLac 100 (co-processed lactose with MCC) gives better results compared to lactose and MCC alone. This may be due to the combination of plastic with fragmentally deforming materials, leading to improved compaction and tablet properties.

To better understand the observations, X-ray microtomographic images of Compritol® 888 ATO tablets were taken (Figure 4-4). This technique enables the observation of the pores (black zone), before and after 6 h of dissolution. In the case of DCP (Figure 4-4a), a porous zone is observed at the edges of the tablet after 6 h of dissolution. With lactose (Figure 4-4b), the porous zone is much wider and extends to the center of the tablet. This study confirms that the dissolution of the diluents plays a key role in modulating drug diffusion from the Compritol matrix.

In Compritol 888 ATO matrix tablets made by direct compression, water-soluble diluents will affect drug diffusion into the aqueous media.

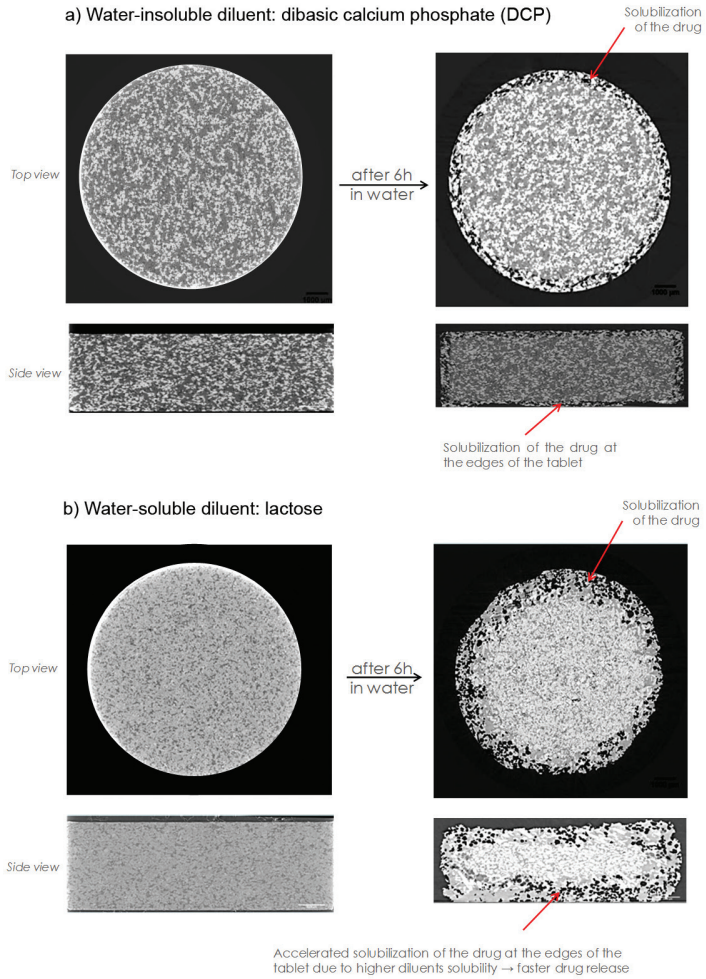


Figure 4-4 X-ray microtomographic images of Compritol® 888 tablets containing: a) water-insoluble and b) water-soluble filler before and after 6 h of dissolution in phosphate buffer 4.5 at 37 °C (30% drug, 19.5% Compritol® 888, 50% filler, 0.5% magnesium stearate, tablet weight 333.3 mg, direct compression process)

3. Change the surface area of the matrix

In diffusion-driven drug release, the dimension of the dosage form correlates with the drug release rate: the length of the diffusion pathway determines the release kinetics. This is shown in Figure 4-5, with the schematic representation of the drug diffusion pathway for tablets of 12 mm diameter and 3.8 mm height (bottom) and 14 mm diameter and 4.8 mm height (top). Increasing the diffusion pathway leads to longer water penetration times. Therefore, the adjustment of tablet dimensions provides scope to optimize the drug release profile.

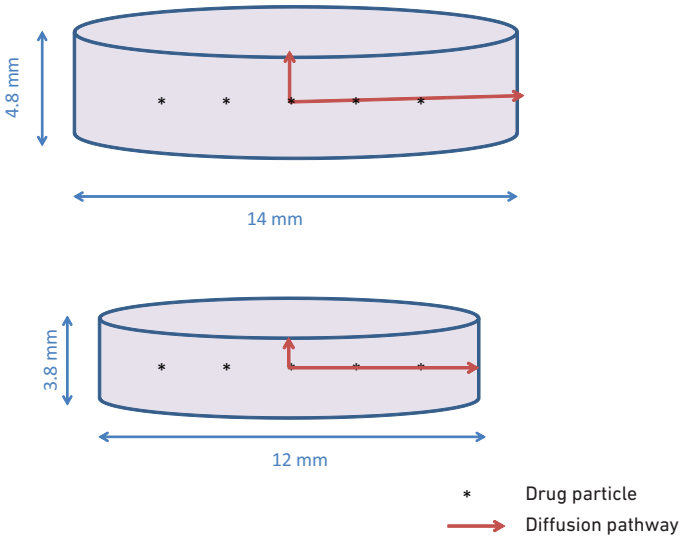


Figure 4-5 Schematic representation of the effect of tablet size on the length of diffusion pathway

With theophylline tablets (Figure 4-6) when tablet weight (500 mg) and drug dose remain identical but the tablet diameter and height are altered, the drug release profile changes. This demonstrates that tablet dimensions impact drug dissolution: **the higher the specific surface area, the slower the drug release.**

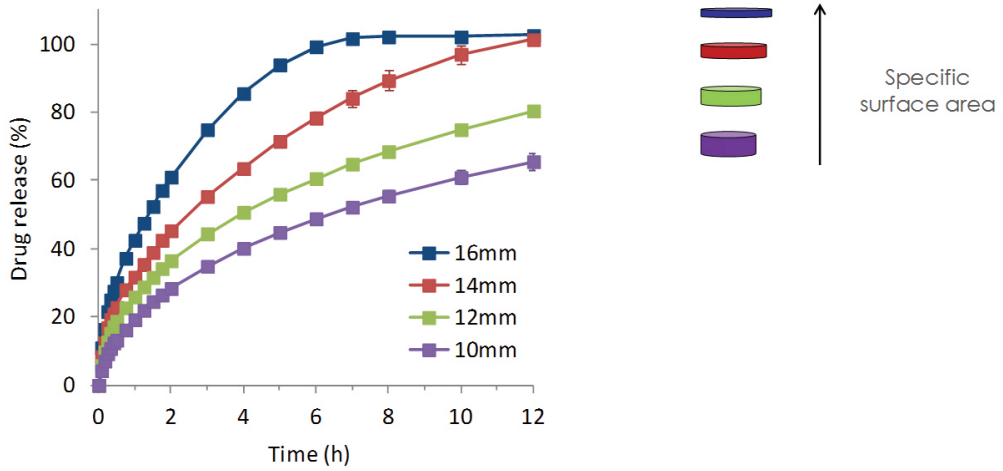


Figure 4-6 Effect of the specific surface area of the tablet on drug release (20% theophylline, 15% Compritol 888, 65% dibasic calcium phosphate:lactose 1:1, 0.5% magnesium stearate, tablet weight constant at 500mg, direct compression process)

4. Change drug particle size

Increasing drug particle size results in smaller particle specific surface and reduced contact area with aqueous medium, leading to reduced drug release. Consequently, formulating with a different drug particle size is a means of changing the drug release kinetic.

5. Change the process

Cold processes such as direct compression (DC) or wet granulation (WG) are suitable for the production of Compritol® 888 ATO matrix tablets. Alternatively, melt processes generally deliver significantly slower drug release rates due to the entrapment of drug within the lipid.

Tablets of identical composition prepared by different techniques (direct compression, wet granulation or hot melt extrusion) were produced for three different model drugs: niacin, metoprolol succinate and metformin HCl (Figure 4-7). Tablets obtained by DC and WG have similar drug release profiles, although the wet granulation process provides tablets with better tensile strength (Table 4-4). Tablets produced by hot melt extrusion deliver a much slower rate of drug release.

Table 4-4 Tensile strength of tablets prepared by direct compression, wet granulation or hot melt extrusion

Tensile strength (MPa)	Direct compression	Wet granulation	Hot melt Extrusion
Niacin	0.73	1.42	1.09
Metoprolol succinate	0.87	1.36	1.13
Metformin HCln	0.44	1.52	0.90

READ MORE

The effect of process on drug release of Compritol® 888 ATO sustained release tablets: direct compression, wet granulation and hot melt extrusion.

CRS poster
Rosiaux Y. et al, 2014c.

a) Niacin

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

b) Metoprolol succinate

Ingredients	Quantity (%)
Metoprolol succinate	33.3
Compritol® 888 ATO	40
Povidone	5
Lactose	16.7
AL_2O_3-MgO-SiO_2	3
SiO_2	1
Mg stearate	1
Tablet weight	600 mg

c) Metformin HCl

Ingredients	Quantity (%)
Metformin HCl	50
Compritol® 888 ATO	30
Povidone	5
DCPA	11
SiO_2	3
Mg stearate	1
Tablet weight	1000 mg

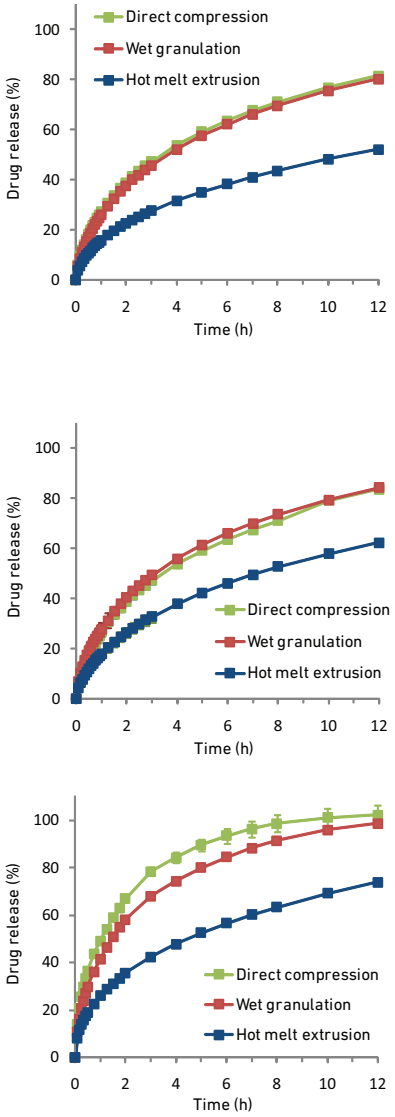


Figure 4-7 Effect of the process on drug release from Compritol® 888 ATO matrix tablets (Rosiaux et al, 2014c)

Cold versus hot melt process

In a hot melt process drug is embedded within the Compritol® 888 ATO matrix tablet. Wetting and drug diffusion are greatly reduced, and water is prevented from penetrating the matrix, slowing down the development of new pores and water channels through which the drug can diffuse out. Drug dissolution and diffusion is thus extended, resulting in a slower release profile (Figure 4-8).

Cold process

Hot process

Reduced wettability compared with cold processed tablets

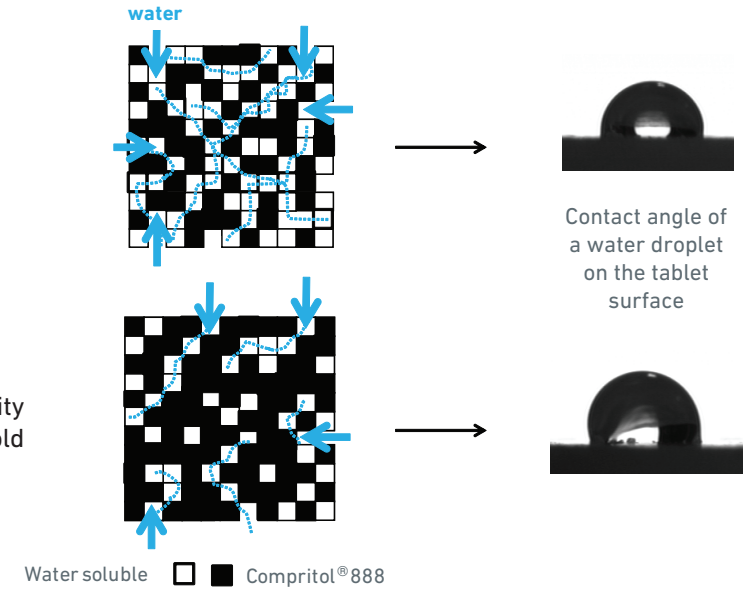


Figure 4-8 Schematic representation of the differences in the drug diffusion process from Compritol® 888 ATO matrix tablets produced by cold or hot processes

If the sustained release profile is too fast with a cold process, a melt process can be considered.

5. Resistance to physiological variations with a good *in vitro - in vivo* correlation

Physiological pH conditions and ionic strength vary along the gastrointestinal (GI) tract. This can have significant impact on drug release from the dosage form if excipients that are sensitive to pH variations are used. **Compritol® 888 is non-ionic and inert and therefore its behavior is independent of pH conditions**

5.1 In vitro digestion in biorelevant media and static conditions

Digestion is known to affect drug dissolution when excipients that are 'digestible' are used. A fed state induces lipid digestion, i.e. lipases hydrolyze the lipid ester bonds generating monoglycerides and free fatty acids. However, Compritol® 888 is not digestible when it is delivered in a monolithic form (Figure 5-1) due to its composition of long, saturated C_{22} fatty acids.Therefore good correlation between *in vitro* and *in vivo* drug release from Compritol® 888 matrix tablets can be expected.

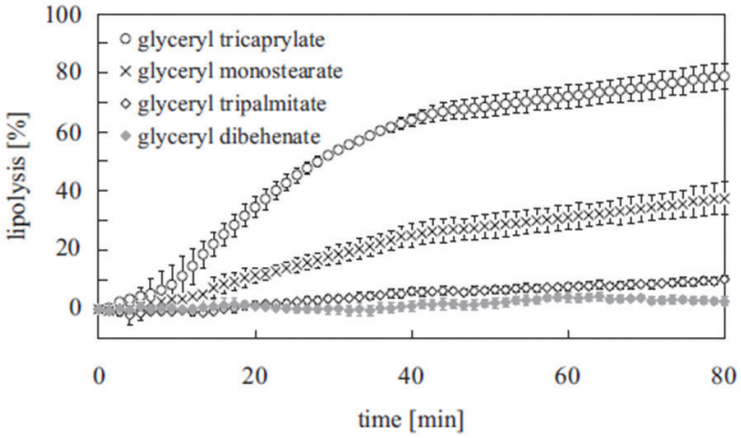


Figure 5-1 In vitro lipolysis of Compritol® 888 (glyceryl dibehenate) and other lipid excipients in extrudates with 50% praziquantel (reprinted from Witzleb, 2012)

5.2 In vitro digestion in biorelevant media and dynamic conditions (modified USP method by Garbacz)

Standard (USP) *in vitro* dissolution methods are not discriminative regarding the performance of a dosage form and drug release properties in *in vivo* physiological conditions (this is true for all sustained release matrix tablets). The dosage form is subject to gastrointestinal motility and different fluid volumes in the human GI tract. In addition significant pressure is present during transit from one compartment to another. Together, these conditions result in discontinuous movement behavior with interrupted contact of the dosage form with the release medium.

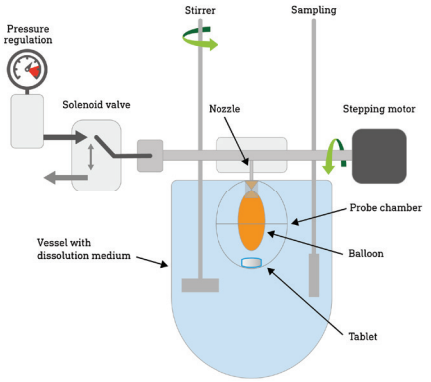


Figure 5-2 Principle of the stress test device apparatus according to Garbacz

To highlight **the robustness of Compritol® 888 ATO tablets** a study was undertaken at the University of Greifswald using an adjusted version of the USP II method as described by Garbacz et al. (2008). This specific apparatus (Figure 5-2) simulates the gastrointestinal pressure waves and the discontinuous contact of the dosage form with the body fluid.

- The artificial pressure acting on the dosage form is developed by a balloon inflating at pre-determined time points (referred to gastrointestinal transit).
- Low body volumes and discontinuous contact with the fluid is simulated by continuously dipping the "stressed" dosage form into the release medium, as opposed to being permanently exposed to aqueous fluid.

With Theophylline in Compritol® 888 ATO matrix tablets (300 mg) a slower release rate is observed between the gastric emptying (GE) and ileocecal phase (ICP) in fed state biorelevant media using a stress test device compared with the fasted state biorelevant media (Figure 5-3).

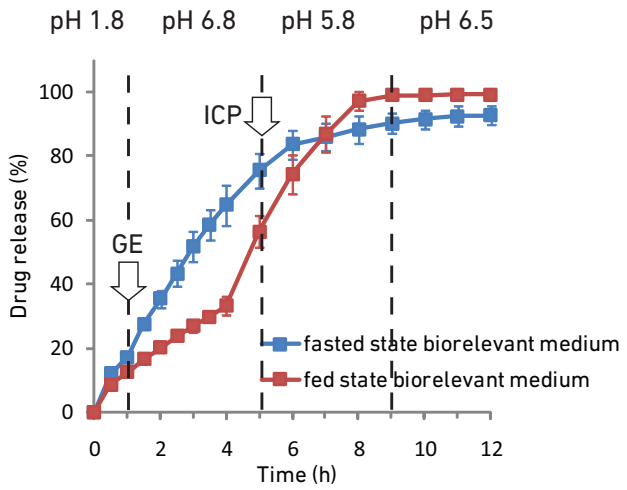


Figure 5-3 In vitro dissolution testing in fasted and fed state biorelevant media using a stress test device with simulated pressure waves, pH changes and rotational movement (33.3% theophylline, 20% Compritol® 888, 45.17% Pharmatose DCL11, 1% Aerosil 200 Pharma, 0.5% magnesium stearate, tablet weight 300 mg, direct compression process) GE = gastric emptying (first pressure wave of 3x300 mbar), ICP = ileocecal passage (second pressure wave of 3x300 mbar),rotational movement at 100 rpm

The difference in release rate in fed versus fasted media is possibly attributable to the high viscosity of the simulated fed state milieu (worst case scenario with standard breakfast substitute). In addition, pH changes, rotational movement and applied pressure waves simulating gastrointestinal passage and motility do not result in changes in drug diffusion.

This study highlights the robustness of Compritol 888 ATO matrix tablets in more biorelevant conditions.

READ MORE

Estimating *in vivo* drug release from a new theophylline Compritol® 888 ATO matrix formulation using appropriate biorelevant test methods.

CRS poster
Klein S. et al, 2014.

5.3 Good *in vivo-in vitro* correlation (IVIVC)

An *in-vivo* study evaluating the IVIVC of metoprolol succinate in Compritol 888 ATO SR tablets has been undertaken by Gattefossé and the Bombay college of Pharmacy (Patere et al, 2013).

The metoprolol succinate SR tablet was designed to deliver the same drug release profile as a market approved tablet made with HPMC widely prescribed in India. The optimized formulation (Table 5-1) was made using a melt & mix hot process: metoprolol succinate and MCC were dispersed into melted Compritol® 888 ATO; after cooling granules were made and compressed into tablets. The dissolution of metoprolol succinate from the Compritol® SR tablets was equivalent to that of the market reference (Figure 5-4).

Table 5-1 Composition of Compritol® SR tablets

Ingredient	Quantity (%)	
	% w/w	mg/tablet
Metoprolol succinate	28.55	50
Compritol® 888ATO	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

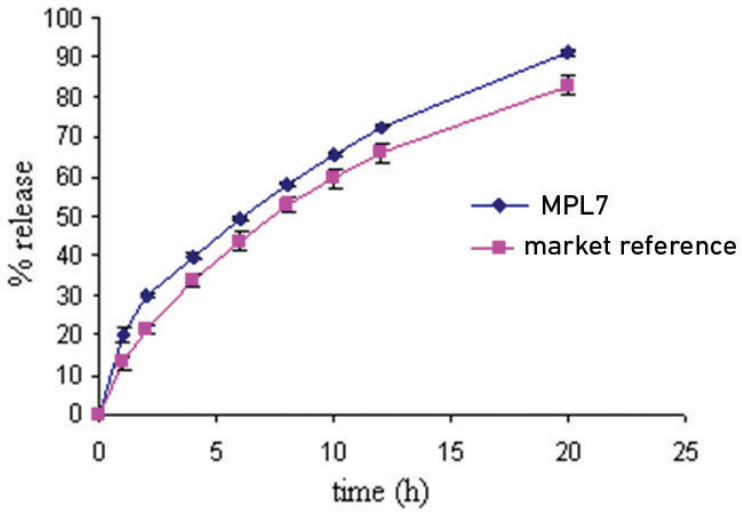


Figure 5-4 In vitro dissolution of metoprolol succinate release from Compritol 888 tablets and market reference

Bioequivalence between the Compritol® ATO matrix tablets and the market reference was established using the correlation between the *in vitro* release pattern and the *in vivo* results in 12 healthy human volunteers. A randomized, single dose, two-treatments, two periods, cross-over study with a washout period of 15 days was employed. All the study procedures were performed according to the protocol approved by Institutional ethics committee (EC/Pharm-28/2010). The average values obtained *in-vivo* for both formulations were found to be comparable (Table 5 2).

Figure 5-5 confirms the excellent IVIVC of metoprolol succinate in Compritol® 888 ATO SR tablets.

Table 5-2 Pharmacokinetic parameters of Compritol® and market formulations

Parameter	Compritol® formulation	Market reference
C_{max} (ng/mL)	30.97 ± 11.88	29.90 ± 11.07
T_{max} (h)	4.33 ± 2.28	5.16 ± 1.91
Cumulative AUC (ng.h/mL)	454.96 ± 193.82	372.68 ± 128.22

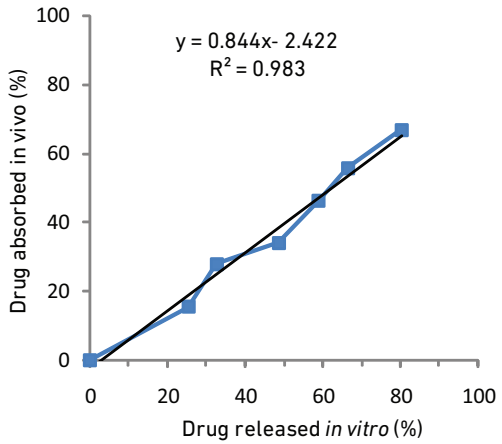


Figure 5-5 In vitro-in vivo correlation of metoprolol succinate release from Compritol® 888 tablets (28.55% metoprolol succinate, 57.11% Compritol 888, 11.42 Avicel PH-101, 0.97% Aerosil 200 Pharma, 1.94% magnesium stearate, tablet weight 175.1 mg, melt granulation process)

6. Case studies

6.1 High dose tablets with a medium solubility API, eg niacin

The production of high dose SR matrix tablets is challenging; often the flow and compactability of micronized drugs is poor. Three formulation approaches of high dose niacin SR matrix tablets with Compritol® 888 ATO are presented in the following study.

a) 500 mg niacin tablets by direct compression

The niacin powder was micronized (mean particle size 34 µm) and had poor flowability. The addition of a glidant was necessary to provide continuous die filling and homogenous content uniformity in a direct compression process (Table 6-1).

Table 6-1 Tablet formulation with 500 mg niacin in direct compression

Ingredients (%)	% w/w	mg
Niacin	63	500
Compritol® 888 ATO	20	159
Emcompress Premium	14.5	115
Aerosil 200 Pharma	1.5	12
Magnesium stearate	1	8
Total	100	794

Tablets were produced using a 10 station rotary press (Riva Piccola Euro B, Argentina) equipped with 12 mm flat punches. Compression force was 15 kN, compaction speed 50 rpm. Tablet properties were as follows.

- tablet weight 786.6 ± 4.6 mg
- average weight variation 0.5%
- content uniformity 473.8 ± 11.2 mg
- tensile strength 1.32 MPa

Drug release rate from the tablets is shown Figure 6-1.

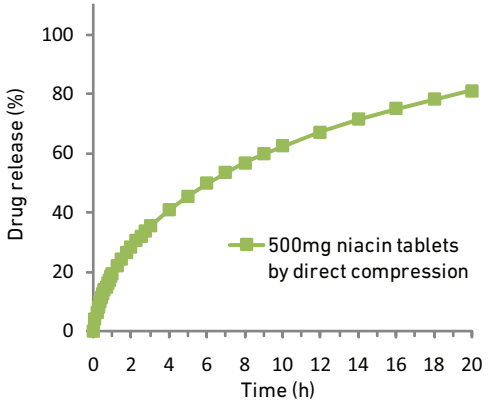


Figure 6-1 Niacin release from Compritol® 888 ATO matrix tablets prepared by direct compression (USP monograph niacin extended release tablets)

b) 1000 mg niacin tablets by wet granulation

The niacin formulation was granulated prior to compression to improve powder flow and compactability (Rosiaux et al, 2015a). In this formulation the addition of a glidant was not necessary (Table 6-2).

Table 6-2 Tablet formulation with 1000 mg niacin in wet granulation

Ingredients (%)	% w/w	mg
Niacin	71.6	1000
Compritol® 888 ATO	17.9	250
Kollidon 30 (PVP)*	10	140
Magnesium stearate	0.5	7
Total	100	1397

** PVP was added in dry powder form prior to fluid bed granulation with water*

Tablets were produced using a single station press (Korsch EK0, Germany) equipped with 16 mm flat punches. Compression force was 14 kN, compaction speed 30 tablets/min. Tablet properties were as follows.

- tablet weight 1401.8 ± 4 mg
- average weight variation 0.3%
- tensile strength 1.62 MPa

Drug release rate from the tablets is shown Figure 6-2.

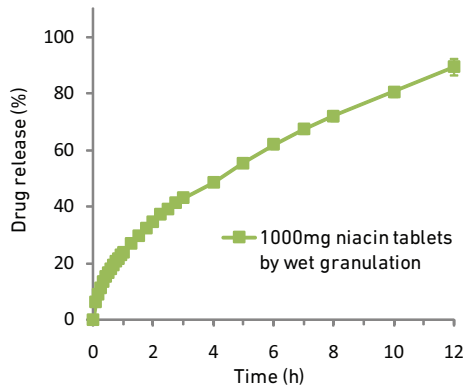


Figure 6-2 Niacin release from Compritol 888 matrix tablets prepared by wet granulation (USP monograph niacin immediate release tablets)

c) 326.5 mg niacin tablets by hot melt extrusion

The niacin powder was extruded with Compritol® 888 ATO at a feed rate of 200 g/h, screw speed of 100 rpm and extrusion temperature of 60-63-68-70-68-70-70-71 °C from feed to die (In-house data). Dissolution testing was performed with both milled extrudates and milled extrudates compressed into tablets (Table 6-3).

Table 6-3 Granules and tablet formulation using hot melt extrusion

Ingredients (%)	%w/w granules	% w/w tablets	mg tablets
Niacin	60	65.3	326.5
Compritol® 888 ATO	40	21.8	109
Flowlac 100	-	12.4	62
Magnesium stearate	-	0.5	2.5
Total	100	100	500

The extrudates were milled through a 1600 µm screen using an oscillating granulator (Erweka AR401, Germany). Tablets were produced from the granules using a single station press (Korsch EK0, Germany) equipped with 12 mm flat punches. Compression force was 5-6 kN and compaction speed 30 tablets/min. Tablet properties were as follows

- tablet weight 507.1 ± 2.4 mg
- average weight variation 0.5%
- tensile strength 1.05 MPa

Release rates from the granules and tablets are shown in Figure 6-3

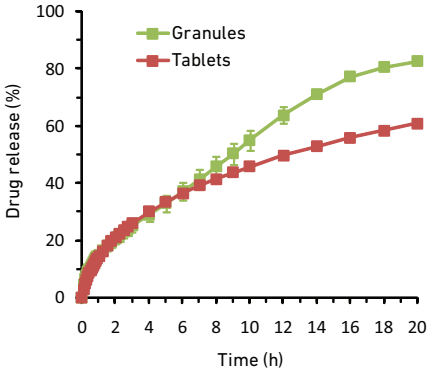


Figure 6-3 Niacin release from Compritol® 888 ATO matrix granules and tablets prepared by HME (USP monograph niacin extended release tablets)

6.2 High dose tablet with a highly soluble API, eg Metformin HCl

The metformin HCl powder has a solubility of 335 mg/mL at 37 °C in phosphate buffer pH 6.8. The required drug dose was 500 mg and drug compactability was poor. To provide homogenous content uniformity the addition of a glidant (Aerosil) was required. Emcompress was used to provide sufficient tablet hardness (Table 6-4).

Table 6-4 Tablet formulation with 500mg metformin HCl in direct compression

Ingredients (%)	% w/w	mg
Metformin HCl	50	500
Compritol® 888 ATO	30	300
Emcompress Premium	18	180
Aerosil 200 Pharma	1	10
Magnesium stearate	1	10
Total	100	1000

Tablets were produced using a 10 station rotary press (Riva Piccola Euro B, Argentina) equipped with 14 mm flat punches. Compression force was 17 kN, compaction speed 50 rpm. Tablet properties are described below.

- tablet weight 991 ± 6.7 mg
- average weight variation 0.8%
- content uniformity 494.8 ± 5.2 mg
- tensile strength 0.77 MPa

Drug release rate from the tablets is shown in Figure 6-4

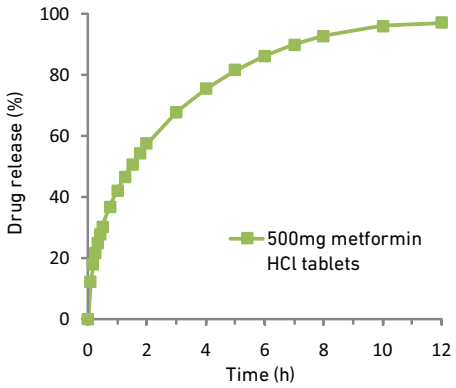


Figure 6-4 Metformin HCl release from Compritol® 888 ATO matrix tablets prepared by direct compression (USP monograph metformin extended release tablets)

6.3 Medium dose tablet with a highly soluble API, eg Bupropion HCl

Bupropion HCl solubility was measured as 330 mg/mL at 37 °C in water. The required drug dose was 150 mg and drug compactability was poor. The formulation required a glidant (Aerosil) to prevent sticking and Microcelac 100 was added to increase tablet hardness. Cysteine was used to prevent drug degradation (Table 6-5).

Table 6-5 Tablet formulation with 150mg bupropion HCl in direct compression

Ingredients (%)	% w/w	mg
Bupropion HCl	43	150
Compritol® 888 ATO	30	104.6
L-cysteine HCl	2	7
Microcelac 100	23	80.2
Aerosil 200 Pharma	1	3.5
Magnesium stearate	1	3.5
Total	100	348.8

Tablets were produced using a 10 station rotary press (Riva Piccola Euro B, Argentina) equipped with 10 mm concave punches. Compression force was 15 kN, compaction speed 50 rpm. Tablet properties were as follows

- tablet weight 351.4 ± 3.7 mg
- average weight variation 1.1%
- content uniformity 146.6 ± 1.9 mg
- tablet hardness 86.3 N
- friability 0.17%

Drug release rate from the tablets is shown in Figure 6-5.

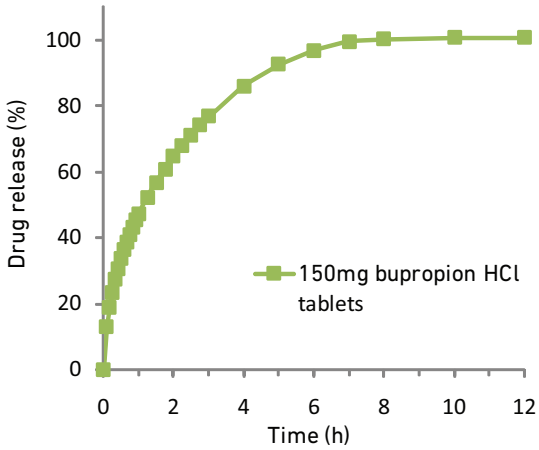


Figure 6-5 Bupropion HCl release from Compritol® 888 ATO matrix tablets prepared by direct compression (USP monograph bupropion extended release tablets)

6.4 Mini-tablets for special patient needs

Young children and the elderly may experience swallowing difficulties which makes the administration of conventional tablets a challenge due to their size and form. Sometimes tablets are cut or crushed into smaller parts to facilitate administration. However, controlled release formulations (SR, ER, pulsed, timed etc) should not be modified as this alters the drug release rate. Mini-tablets provide scope to deliver the benefits of SR tablets to patients with swallowing difficulties; their small size facilitates swallowing and reduces the likelihood of tablets being split or crushed.

However, developing SR mini-tablets is challenging as the drug diffusion pathway is reduced and therefore drug diffusion is accelerated. Higher Compritol® 888 ATO concentrations are required to achieve the target release rates (Table 6-6, Figure 6-6).

Table 6-6 Mini-tablet formulation with Compritol 888 in direct compression

Ingredients (%)	Theophylline	Levodopa
Drug	16.7	37.5
Compritol® 888 ATO granules*	35	25
Fujicalin SG	29.5	22.35
Pharmatose 200M	14.8	11.15
Neusilin US2	3	3
Magnesium stearate	1	1
Tablet production	*Stylcam®100R*	*Stylcam®100R*
Tablet weight (mg)	*7.5*	*20*
Tablet size (mm)	*2*	*3*

** Compritol® 888 ATO granules were made by melt-grind method to improve flowability*

Compritol® 888 ATO is an effective and interesting SR agent for mini-tablets (≥4 mm)

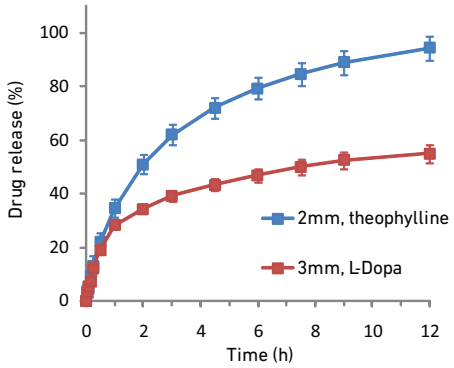


Figure 6-6 Drug release from mini-tablets produced by direct compression (theophylline: 900mL phosphate buffer pH 4.5 in USPII; L-dopa: 900mL demineralized water in USPII)

READ MORE

Formulation effects on drug release and sustained release Compritol® 888 ATO tablets and mini-tablets.

CRS poster
Roberts M. et al, 2011.

READ MORE

Sustained Release Levodopa Mini-Tablets Containing Compritol® 888: A Viable Approach For Special Patient Populations.

AAPS poster
Roberts M., Rosiaux Y., 2013.

6.5 Tablet coating with polymers

Given the lipophilic nature of Compritol 888 ATO, a common question concerns the feasibility of applying a hydrophilic polymer coating to tablets. An in-house study with Opadry® red (Colorcon) in a pan-coating method was undertaken. Placebo Compritol tablets (40%) were sprayed with a 15% (w/w) aqueous solution of Opadry® red to obtain up to 5% coating level by weight.

The coating parameters were as follows:

- Nozzle diameter 0.8 mm
- Drum speed 14 rpm
- Atomization pressure 1.5 bar
- Mean spray rate 2.6 g/min
- Inlet temperature 60 °C
- Product temperature 29 °C

Evaluation of the coated tablets indicated that the coating solution adhered correctly to the tablet core resulting in smooth, defect free coating. The application of a hydrophilic polymer coating is feasible despite the difference in chemical nature to Compritol. (Rosiaux et al, 2014b) (Figure 6-7)

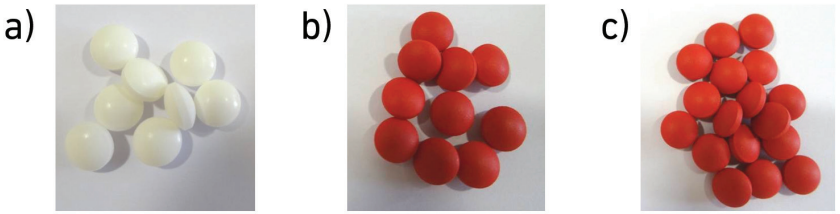


Figure 6-7 Compritol 888 tablets (9mm) coated with Opadry® red: a) uncoated, b) 3% coating weight gain, c) 5% weight gain (40% Compritol® 888 ATO, 36% Emcompress Premium, 23.5% Supertab® SD 11 and 0.5% magnesium stearate, direct compression process)

READ MORE

Color coating of Compritol® 888 ATO matrix tablets a feasibility study

AAPS poster
Rosiaux et al, 2014b.

7. Trouble shooting

7.1 Insufficient tablet hardness

Tablet hardness can be compromised when Compritol® 888 ATO is used at higher concentrations due to its crystalline nature and its spherical and smooth lipophilic particles. At high concentrations the development of solid bridges, hydrogen and covalent bonds is reduced leading to low inter-particulate cohesion.

Tablet hardness can be improved by the addition of appropriate diluents/fillers (Figure 7-1). At Gattefossé the following excipients are routinely used.

- MCC - including Avicel PH-101/102, MicroceLac 100, Vivapur 102, Prosolv
- DCP such as Emcompress or lactose grades with good compaction properties
- Neusilin can be used as a processing aid
- Avicel PH-200 should be avoided - in Compritol tablets it can induce tablet splitting during dissolution.

Reducing compaction speed to increase the dwell time, thus the compaction length per tablet provides better particle cohesion and stronger tablets. An increase of compaction force might be feasible, but the effect levels off between 15 and 20 kN.

Alternatively wet granulation with a binder (HPMC or PVP) can be used to increase tablet hardness.

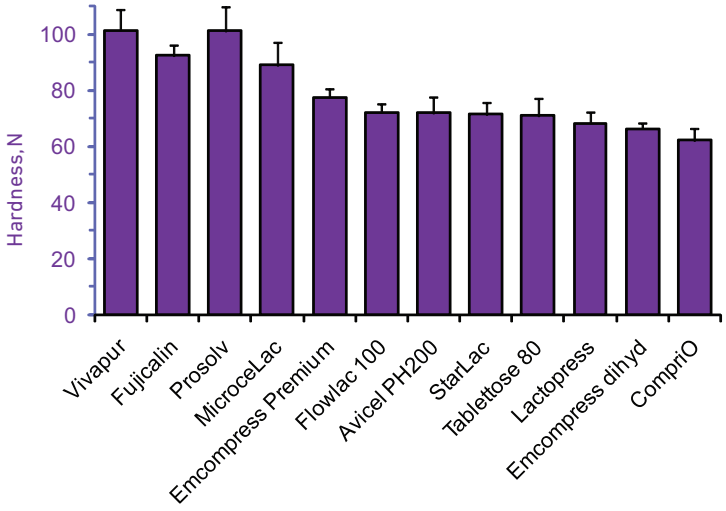


Figure 7-1 Effect of different fillers on the hardness of Compritol® 888 ATO matrix tablets (30% theophylline, 19.5% Compritol® 888 ATO, 50% filler, 0.5% magnesium stearate,tablet weight 333.3mg, direct compression process)

7.2 Sticking during compression

Sticking during tableting is a relatively common problem in tablet manufacturing. Two different types of 'sticking' are described below along with remedial actions.

Sticking isolated to specific areas of the punch, mainly on the upper punch, is referred to as spot-sticking. If this occurs the first action is to verify the quality of the tooling and the machine set-up. Spot-sticking is most commonly associated with the equipment and process and not the formulation properties.

Sticking occurring on the entire punch surface (upper or lower) is referred to as 'filming'. If this occurs and machine set-up optimization does not overcome the problem then reformulation may be required.

The following decision tree (Figure 7-2) helps to determine the parameters that can be changed to prevent or resolve sticking problems.

Gattefossé undertook an in-house study to investigate the main causes of 'sticking' during the compression of powder formulations containing Compritol® 888 ATO as an SR agent. Metoprolol succinate was the model drug as it is known to be sticky. The study was designed to discriminate whether the API or Compritol® 888 ATO was the primarily cause of sticking by sequentially replacing each ingredient with lactose.

Tablets were prepared with metoprolol succinate (mean particle size 51µm). Since powder flow of the formulation was poor a process of wet granulation was applied to increase particle size and improve flowability. The final tablets contained 40% metoprolol succinate, 40% Compritol® 888 ATO, 5% PVP (intra-granular) and 11% DCPA, 3% Neusilin, 1% magnesium stearate (extra-granular). In addition, a series of tableting tests were performed on formulations in which Compritol® 888 ATO or metoprolol was replaced by lactose, to determine which of the ingredients was causing sticking.

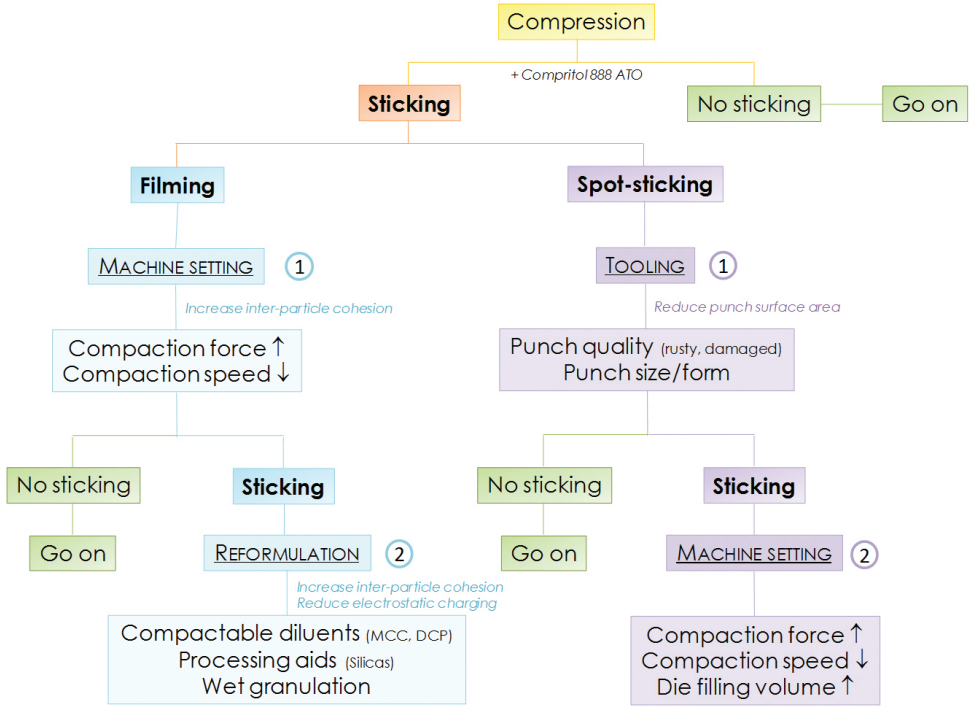


Figure 7-2 Schematic approach to address sticking issues in compression

The state of the punches was evaluated after each tableting series. The formulation containing metoprolol succinate and Compritol® 888 ATO led to sticking (Figure 7-3). Substitution of metoprolol succinate with lactose, whilst maintaining the same Compritol® 888 ATO concentration resolved the sticking problem (Figure 7-4). Substitution of Compritol® 888 ATO with lactose, whilst maintaining the same metoprolol succinate concentration again resulted in sticking (Figure 7-5).

Figure 7-3 White traces visible with metoprolol:Compritol® 888

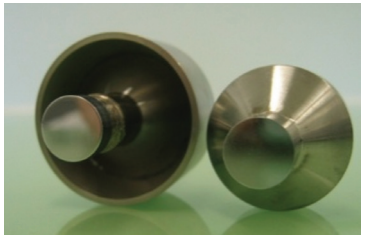


Figure 7-4 Clean punches with metoprolol-free formulation

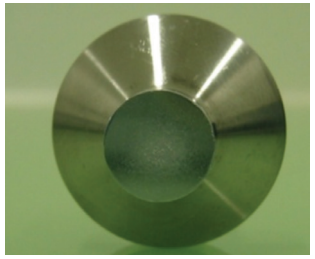


Figure 7-5 White traces visible with Compritol® 888 ATO-free formulation

In this study, it appeared that sticking was primarily associated with the active ingredient and not with Compritol® 888 ATO

7.3 Alcohol induced dose dumping

Alcohol induced dose dumping from extended release formulations has become an important safety concern especially for certain types of API including highly potent drugs. Dose dumping can be caused by the unintended dissolution of the functional excipient (generally alcohol-soluble polymer) in the hydroalcoholic media resulting in immediate drug release.

For certain drug products, regulatory authorities (eg. USA FDA) require *in-vitro* dissolution tests in the presence of increasing ethanol concentrations to be performed to evaluate the potential effects of alcoholic beverages on drug release kinetics.

Compritol® 888 ATO is not soluble in alcohol and therefore the release retarding matrix is not affected by hydroalcoholic media. However, **if drug solubility changes in the presence of alcohol, this can significantly modify diffusion from the matrix.**

For illustration, two model drugs were used (Table 7-1):

- Theophylline, more soluble in 40% ethanol than in 0.1N HCl:
- Niacin, less soluble in ethanol than in HCl.

Table 7-1 Drug and excipient solubility (mg/mL) in ethanol containing aqueous media

Drug	0.1N HCl	0.1N HCl:40% ethanol
Theophylline	11.5	31.6
Niacin	32.3	15.3
Diluent choice to compensate		
MCC	Insoluble	Insoluble
Lactose	250 (40 °C)	60 (40 °C)
DCP	Sparingly	Insoluble
EC	Practically insoluble	Freely soluble

When theophylline is formulated in a Compritol® 888 ATO matrix with MCC, drug release is faster in 0.1N HCl: 40% ethanol than in 0.1N HCl (Figure 7-6a). Such undesired rapid drug release in hydroalcoholic fluid can be prevented by using a diluent that is less soluble in ethanol than in HCl: e.g. lactose. Theophylline release in a Compritol® 888 ATO/lactose matrix is similar in both media (Figure 7-6b).

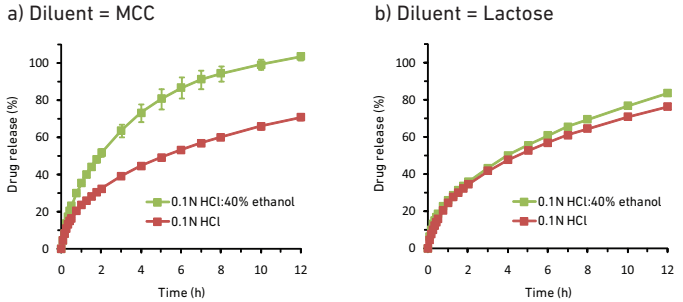


Figure 7-6 Effect of the diluents and the hydro-alcoholic media on the release kinetics of theophylline DC tablets (30% theophylline, 19.5% Compritol® 888 ATO, 50% diluent, 0.5% magnesium stearate, tablet weight

The opposite occurs with niacin which exhibits twofold less solubility in 0.1N HCl: 40% ethanol compared to 0.1N HCl (Table 7-1).

This results in slower release kinetics when DCP is the filler (Figure 7-7a). The release kinetics can be adjusted by adding an ethanol-soluble filler such as ethylcellulose to the formulation, which counterbalances the reduced solubility of niacin (Figure 7-7b).

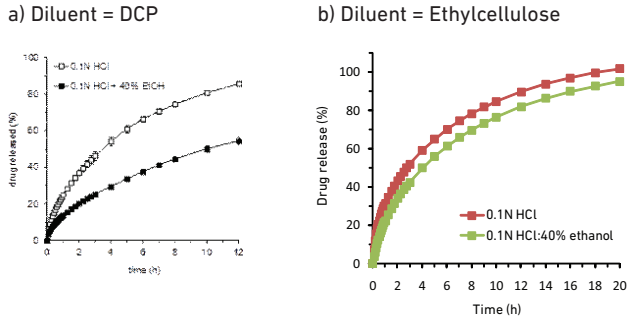


Figure 7-7 Effect of the diluents and the hydro-alcoholic media on the release kinetics of niacin DC tablets (63% niacin, 20% Compritol 888 ATO, 15% diluent, 1.5% Aerosil 200, 0.5% magnesium stearate, tablet weight 794mg, direct compression process)

7.4 Drug release changes during stability testing

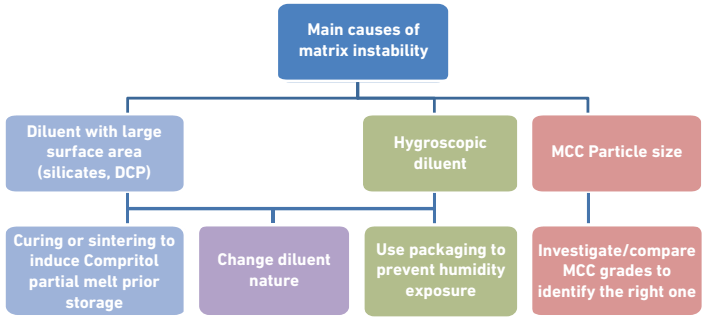
Generally, Compritol 888 ATO SR matrix tablets are stable under standard long-term storage conditions. However certain formulations may exhibit instability under certain stability testing conditions (high temperatures and high humidity).

Since Compritol is inert it is highly compatible with API - as such stability issues are generally not associated with an API-excipient interaction. Recent studies in Gattefossé labs provides evidence that changes in drug release are caused by alterations in the matrix structure over-time - which are associated with the nature of the diluent. Therefore in this section we explain the causes of instability and remedial actions that can be taken.

The polymorphic nature of Compritol® 888 ATO is often considered responsible for changes in drug release kinetics over time. However, a new study shows that although Compritol® 888 ATO can undergo post-processing polymorphic change, this evolution of crystalline structure is not responsible for the changes observed in drug release from tablets made by direct compression (Jannin et al, 2015; Rosiaux et al, 2015b).

In a Compritol 888 matrix drug diffusion kinetic is governed by matrix microstructure/porosity. Any changes to the microstructure/porosity over time can impact the stability of the release kinetic. Gattefossé studies of the relationship between diluent and matrix stability in accelerated conditions (40 °C / 75%RH) indicate that the selection of diluent is crucial to ensure long-term stability and in some cases humidity-proof packaging or coating might be necessary.

The schematic below illustrates the main causes of drug release changes during stability testing and solutions.



a) Impact of diluents with large surface area or high porosity

During long-term storage at 40 °C Compritol® 888 ATO can undergo partial melting with the generation of a liquid fraction. In a tablet formulated with a diluent of large specific surface area and high porosity (eg. silicates or DCP), the diluent can interact with the liquid fraction of Compritol leading to a redistribution of the lipid in the matrix. This phenomenon changes the microporosity of the matrix observed by a slower drug release rate.

A reformulation of the matrix by changing the diluent can improve the stability (Figure 7-8).

If the formulation cannot be changed, release rate changes can be prevented by storing tablets below 35 °C, or by inducing lipid redistribution prior to stability testing by applying a tablet curing process (>24h at 50 °C) or sintering (15-30 min at 80 °C).

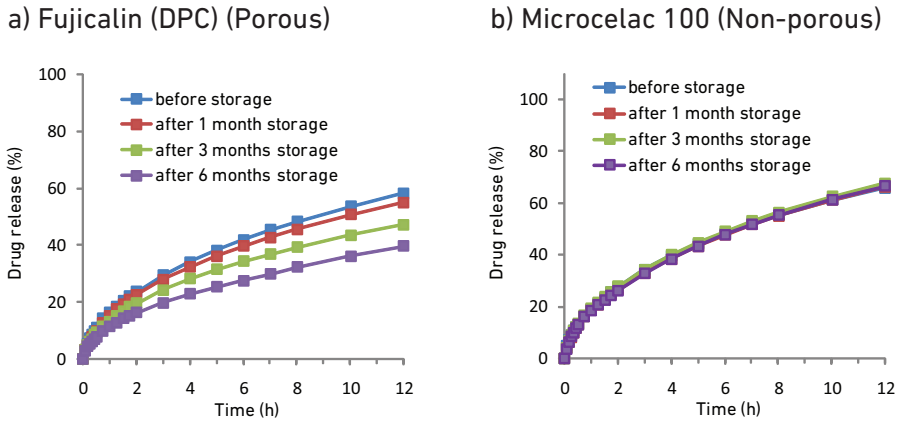


Figure 7-8 Effect of diluent nature on theophylline release from tablets under accelerated storage at 40 °C (30% theophylline, 19.5% Compritol 888, 50% diluent, 0.5% magnesium stearate, tablet weight 333.3 mg, direct compression process)

b) Impact of hygroscopic diluents

Hygroscopic diluents can absorb moisture during storage under accelerated conditions, i.e. 75% RH. Due to moisture uptake and changes in the microporosity of the matrix, the wettability of the dosage form changes during storage overtime altering drug release rate (Figure 7-9a).

The simplest ways to prevent this is to avoid using such excipients with Compritol 888 ATO and/or undertake stability testing/storage in packaging which prevents exposure to humidity (Figure 7-9b).

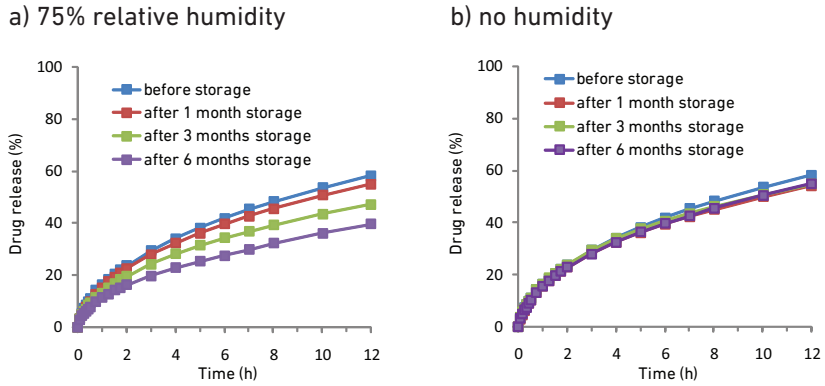


Figure 7-9 Effect of relative humidity on theophylline release from tablets under accelerated storage at 40 °C (30% theophylline, 19.5% Compritol 888, 50% Fujicalin SG, 0.5% magnesium stearate, tablet weight 333.3 mg, direct compression process)

c) Impact of particulate properties of Microcrystalline Cellulose

Microcristalline cellulose (MCC) is available under many types of grades with various particle sizes, density etc... This material can behave differently when it is included into a lipid matrix. Larger particle size can induce lengthwise disruption of the Compritol® 888 ATO matrix (page 14). This can lead to accelerated drug dissolution over time.

In the Figure 7-10, Avicel PH-101 (nominal particle size is 50 µm) gives better stability compared to Avicel PH-200 (nominal particle size is 100 µm). The selection of adapted MCC grades can prevent dissolution changes.

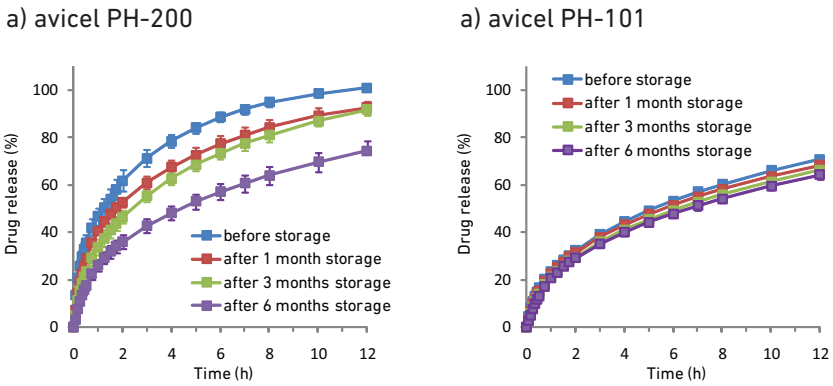


Figure 7-10 Effect of the MCC grade on theophylline release from tablets under accelerated storage at 40 °C/75% relative humidity (30% theophylline, 19.5% Compritol 888, 50% filler, 0.5% magnesium stearate, tablet weight 333.3 mg, direct compression process)

8. Bibliography

Garbacz G., Wedemeyer R. S., Nagel S., Giessmann T. & Weitschies W. (2008). Irregular absorption profiles observed from diclofenac extended release tablets can be predicted using a dissolution test apparatus that mimics *in vivo* physical stresses. European Journal of Pharmaceutics and Biopharmaceutics, 70(2), 421-428.

Jannin V., Rosiaux Y., Doucet J. (2015). Exploring the possible relationship between the drug release of Compritol®-containing tablets and its polymorph forms using micro X-ray diffraction. J Control Release. Jan 10; 197:158-164.

Klein S., Fotaki N., Long C. M., Rosiaux Y., Marchaud D., Garbacz G., Lange S. (2014) Estimating *in vivo* drug release from Theophylline Compritol 888 ATP matrix formulation using appropriate biorelevant test methods.

Patere S. N., Desai N. S., Jain A. S., Kadam P. P., & Nagarsenker M. S. (2013). Compritol® 888 ATO a lipid excipient for sustained release of highly water soluble active: formulation, scale-up and IVIVC study. Current drug delivery, 10, 548-556.

Roberts M., Vellucci D., Mostapha S., Miolane C., Marchaud D. (2011) Formulation effects on drug release and sustained release Compritol 888 ATO tablets and mini-tablets (CRS poster).

Roberts M., Messina M., Mostapha S., Cuppock Y. (2013) Sustained Release Levodopa Mini-Tablets Containing Compritol® 888: A Viable Approach For Special Patient Populations (AAPS poster).

Rosiaux Y., Girard J. M., Desvignes F., Miolane C. and Marchaud D. (2013). Percolation threshold of Compritol® 888 in matrix tablets: assessing the minimum concentration to create an infinite lipid network. AAPS poster.

Rosiaux et al. (2014a) Is Compritol 888 ATO chemically stable in hot melt extrusion processed at high temperature? AAPS poster.

Rosiaux Y., Muschert S., Marchaud D. (2014b). Colour Coating of Compritol® 888 ATO matrix tablets: A Feasibility Study. AAPS poster.

Rosiaux Y., Desvignes F., Girard J. M., Miolane C., Hughes S. and Marchaud D. (2014c). The Effect of the Process on Drug Release of Compritol®888 Sustained Release Tablets: Direct Compression, Wet Granulation and Hot Melt Extrusion. CRS poster.

Rosiaux Y., Jannin V., Hughes S. and Marchaud D. (2014d). Solid lipid excipients – Matrix agents for sustained drug delivery. J. Controlled Release 198, 18-30

Rosiaux Y., Girard J.M., Desvignes F., Miolane C. and Marchaud D. (2015a) Optimizing a wet granulation process to obtain high-dose sustained-release tablets with Compritol 888 ATO. Drug Dev Ind Pharm. 2015; 41(10):1738-44.

Rosiaux Y., Jannin V., Doucet J., Girard J. M., Desvignes F. and Marchaud D. (2015b). New insights into the stability of SR lipid matrix tablets. AAPS poster.

Witzleb R., Müllertz A., Kanikanti V. R., Hamann H. J. and Kleinebudde P. (2012). Dissolution of solid lipid extrudates in biorelevant media. Int J Pharmaceutics 422, 116-124

GATTEFOSSÉ

www.gattefosse.com

Corporate Headquarters
36 chemin de Genas - CS 70070 - 69804 Saint-Priest Cedex - **France**
+(33) 4 72 22 98 00

People make our name