SR matrix using Compritol® 888 ATO Poster Book (2011-2016)

Poster Book February 2017

Years of development within Gattefossé's Application Laboratories led to the publication of numerous posters in main scientific exhibitions around the globe:

- **AAPS (American Association of Pharmaceutical Scientists)**
- **CRS (Controlled Released Society)**
- **PBP (Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology)**

This Poster Book is the collection of all the posters Gattefossé presented from 2011 to 2016 on Sustained Release (SR) matrix using Compritol® 888 ATO.

Posters are ordered from the most recent one to the oldest. However, you can also use the classification by topic proposed next page.

Use the hyperlinks to navigate in this document:

- **each line of the table is a direct link to the corresponding poster**
- **on each poster, use the Gattefossé logo as a link to revert to the table**

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GATTEFOSSÉ

Classification by topic

Compritol® 888 ATO: A Sustained Release Lipid Matrix for Once a Day Aceclofenac Tablets

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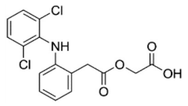
2016 AAPS ANNUAL MEETING AND EXPOSITION
NOVEMBER 13–17, 2016
COLORADO CONVENTION CENTER, DENVER

PURPOSE

ACECLOFENAC (ACF)



Aceclofenac

A glycolic acid ester of diclofenac with four-fold lesser gastric ulcerogenicity

Used in pain and inflammation in arthritic conditions- 100 mg twice daily

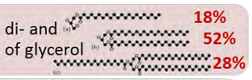
Challenges: Poor water solubility, pH dependent solubility, low compressibility, sticking and picking

A sustained release (SR) once a day ACF formulation is desired for better patient compliance

It is critical to choose appropriate excipients for ACF tablets to address above challenges

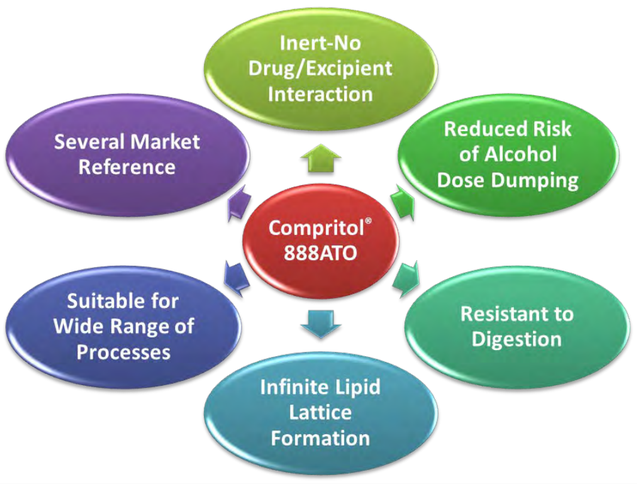
COMPRITOL® 888 ATO: A Versatile SR Lipid Matrix Forming Agent

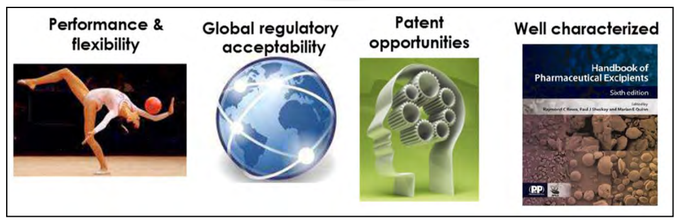
Chemical composition
- Mixture of mono-, di- and tribehenate esters of glycerol



Physical properties
- Fine, white atomized powder of 50µm
- Spherical particles
- Drop point 69 – 74°C
- HLB 1, water insoluble
- Stable over 3 years at < 35°C

Regulatory information
- Conforms to USP/NF/EP/Chinese Ph.
- GRAS, FDA IIG, List of Acceptable Non-medicinal Ingredients





METHOD

WET GRANULATION

ACF-SR tablets were prepared using Compritol® 888ATO as lipid matrix. Table-1 and Fig.-1

To address processing issues various ratios and combinations of Compritol® 888ATO, diluents, lubricants and glidants were evaluated and best compositions are shown in Table-1

Sifting of intragranular ingredients through ASTM #40

ACF + MgO and Compritol® 888ATO - Blending

Addition of other intragranular ingredients - Blending

Wet granulation using PVP K30 solution in RMG followed by drying at 40°C

Table 1: Formulations

Ingredients	Batch-1 % weight	Batch-1 mg/ tab	Batch-2 % weight	Batch-2 mg/ tab
INTRAGRANULAR				
Aceclofenac IP	50.76	200.00	53.33	200.00
Magnesium oxide	1.27	5.00	1.33	5.00
Compritol® 888 ATO	10.15	40.00	9.33	35.00
Avicel® PH101	22.84	90.00	-	-
Mannitol	5.84	23.00	17.33	65.00
Dicalcium Phosphate	-	-	4.00	15.00
PVP K30	3.05	12.00	2.67	10.00
Purified Water	qs	qs	qs	qs
Intragranular Total	**93.91**	**370.00**	**88.00**	**330.00**
EXTRAGRANULAR				
Syloid® 244FP	2.03	8.00	2.13	8.00
Avicel® PH200	-	-	5.60	21.00
Talc	2.03	8.00	2.13	8.00
Magnesium stearate	2.03	8.00	2.13	8.00
Total Tablet Weight	**100.00**	**394.00**	**100.00**	**375.00**

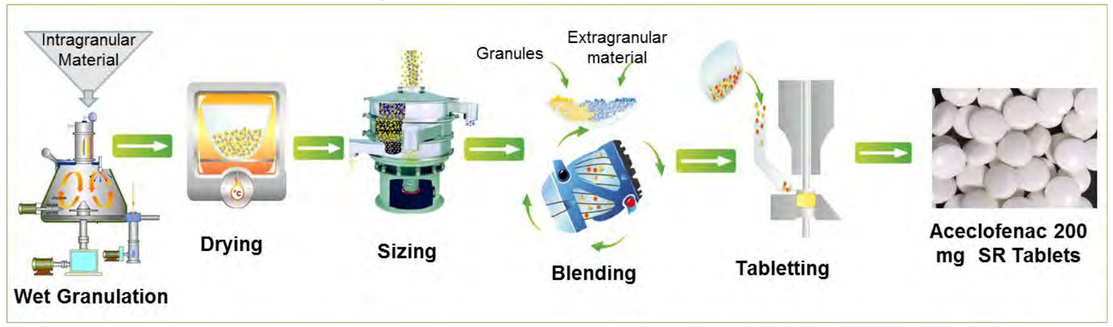
Table 2: Characterization of Granules

Parameters	Batch-1	Batch-2
Moisture content (%)	1.68	1.83
Bulk density (g/mL)	0.425	0.556
Tapped density (g/mL)	0.5	0.654
% Compressibility index	14.97	15.00
Hausner's ratio	1.17	1.18

Compression using 'D' tooling, 9.5 mm round shaped concave, plain punches on fully automated rotary tablet compression machine (Eliza Press)

White colour round shaped tablets were obtained with shiny surface

Fig. 1: Schematic Presentation of Process



EVALUATION OF TABLETS

Physical Evaluation	• Weight variation, Thickness, Hardness, Friability,
Dissolution Study	• Dissolution in 900mL Phosphate buffer pH7.4 , USP Type-II
Alcohol Dose Dumping Study	• Dissolution in 900 mL 0.01N HCl with 10% and 40% ethanol
Analysis	• UV spectrophotometry , λ_{max} 273 nm
Curing Effect	• Curing of tablets at 50°C for 24 h-to study its effect on dissolution

RESULTS

Successful wet granulation of ACF with Compritol® 888ATO was accomplished

Magnesium oxide showed improvement in the flow properties of ACF- static charge neutralization

Granules after sifting through ASTM#25 showed good flow properties

Extragranular excipients further improved the flow property of the granules thus alleviating processing issues

Evaluation of ACF tablets for various parameters are depicted in Table-3

Table 3: Evaluation of Tablets

Test	INITIAL Batch -1	INITIAL Batch-2	Post Curing at 50°C for 24 h Batch -1	Post Curing at 50°C for 24 h Batch-2
Weight of tablets (mg) (n=20)	394±2.0	375±3.2	394±2.2	375±2.8
Thickness (mm)(n=10)	5.3±0.2	5.0±0.2	5.3±0.2	5.0±0.2
Hardness (N)(n=10)	120±10	90±10	140±10	110±10
%Friability (n=20)	0.038	0.046	0.028	0.034
%Drug content (n=10)	99.8±0.6	99.96±0.6	99.9±0.4	99.96±0.6

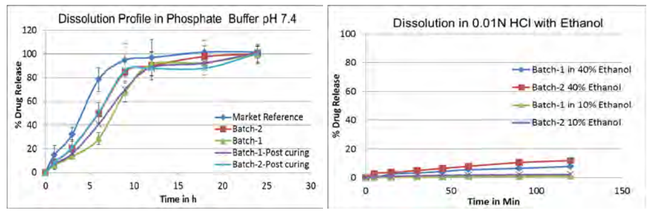
Dissolution of ACF 200 mg tablets of batch-1 and 2 exhibited sustained release up to 18 h (Fig. 2)

Curing of tablets did not affect the dissolution profile, this may be attributed to alkaline microenvironment generated by MgO (Fig. 2)

The release profiles were comparable to a marketed sustained release tablet formulation (Fig. 2)

No alcohol dose dumping was observed in 0.01N HCl with 10% and 40 % ethanol (Fig. 2)

Fig. 2: Dissolution Profile and Dose Dumping Study



CONCLUSION

Compritol® 888ATO as release modifier resulted in successful development of ACF SR 200 mg tablets for once a day pain treatment.

The developed formulation was scaled-up by wet granulation

Alcohol dose dumping was not evident

Curing of tablets was not a necessity

ACKNOWLEDGEMENT

- Grace Davison Chemicals India Pvt. Ltd. for Syloid® 244FP.
- BASF Ltd. for Kollidon® 30.
- Knowell Pharmasolutions for Mannitol.

REFERENCE

- Eur. Patent No:EP2393486 A1.
- Indian Patent No:189/mum/2005.
- Handbook of Pharmaceutical Excipients, 6th Edition.

IMPACT OF HOT AND WET GRANULATION TECHNIQUES ON COMPRITOL® 888 ATO LIPID MATRICES FOR EXTENDED RELEASE OF HIGHLY WATER SOLUBLE HIGH DOSE API

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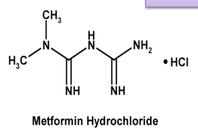
Poster No. 363

INTRODUCTION

Metformin Hydrochloride



Metformin Hydrochloride

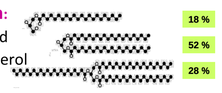
- An oral antihyperglycemic.
- Freely soluble in water,
- Belongs to BCS Class 3
- pKa of 12.4.

- Has a half-life of 6 hours with peak plasma concentrations (Cmax) achieved within one to three hours of taking immediate-release Metformin and four to eight hours with extended-release formulations.
- API possesses poor compaction characteristics and is hygroscopic in nature thereby rendering it difficult to process on an industrial level.

Compritol® 888 ATO: A versatile lipid matrix forming agent

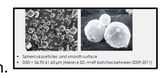
Chemical composition:

Mixture of mono-, di- and tribehenate (C22) of glycerol



Physical properties:

- Fine, white powder of 50 µm
- Spherical particles
- Drop point 69 – 74°C
- HLB 1, water insoluble
- Stable over 3 years at < 35°C

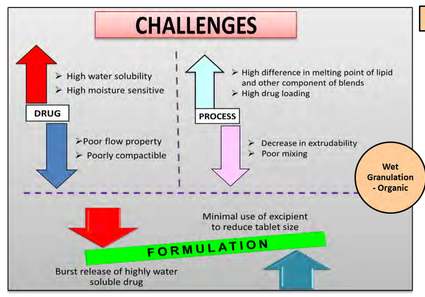


Regulatory information:

- Conform to USP/NF/EP/Chinese Ph.
- GRAS, FDA IIG, List of Acceptable Non-medicinal Ingredient.

OBJECTIVE

To evaluate the impact of different granulation techniques on lipid matrices formed by Compritol® 888 ATO for retarding the release of Metformin Hydrochloride Extended Release Tablets (MHERT) 500 mg.



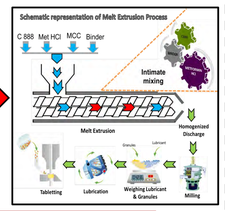
Role of Ingredients	Granulation Process			
	HME	HMG	Wet aqueous	Wet organic
API	Metformin Hydrochloride			
Release Modifier	Compritol® 888 ATO			
Binder	Hydroxy Propyl Cellulose		PVP K30	
Diluent	Avicel® PH 101 (Intragranular) Avicel® PH 200 (Extragranular)			
Extragranular adsorbent	Aerosil® 200			
Glidant	Syloid® 244 FP			
Lubricant	Magnesium Stearate			

EXPERIMENTAL

Hot Melt Extrusion Process

- Instrument name: Pharma 11 Twin screw extruder
- Screw diameter: 11mm
- Length: 90 cm
- L/D ratio: 40:1
- Screw type: Co-rotating parallel twin screw
- Speed: 75 RPM

Thermo Fischer Pharma 11 Twin Screw Extruder

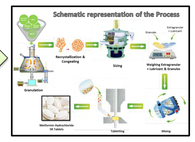


Ingredients	Drug loading (%)							
	F1	F2	F5	F8	F9	F10	F11	F12
Metformin HCl	65	65	65	65	75	75	75	75
Compritol® 888 ATO	25	35	30	25	20	15	10	5
Starch 1500	10	-	-	-	10	-	-	-
Klucel® LF	-	10	-	5	-	10	-	5
Avicel® PH 101	-	-	10	5	-	-	10	5
Temperature (°C)	90	90	100	100	150	120	130	150
RPM	75	75	75	75	75	75	75	75
Torque (%)	30 - 60							

Hot Melt Granulation Process

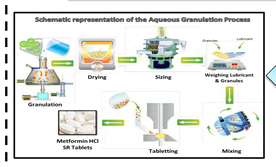
Capacity		5 Litres	2 Litres
Working	Min	2 L	0.8 L
Capacity	Max	4 L	1.6 L
Heating Capacity		Upto 100°C	
MOC		Contact Parts: SS 316 Non- Contact parts: SS 304	
Power Supply		415 V, 3 Phase, 50 Hz	

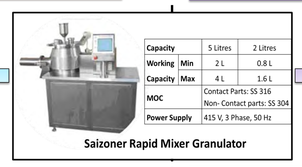
Water Jacketed Saizoner Rapid Mixer Granulator



EXCIPIENTS	% in formula	mg / Tablet
	INTRAGRANULAR EXCIPIENTS	
Metformin Hydrochloride	62.5	500
Compritol® 888 ATO	25	200
Klucel® LF	6	48
Avicel® PH 101	6.5	52
	EXTRAGRANULAR EXCIPIENTS	
Avicel® PH 200	3.53	30
Aerosil® 200	2	16
Magnesium Stearate	0.5	4
Total Tablet Weight		**850**

Wet Aqueous Granulation Process





Capacity		5 Litres	2 Litres
Working	Min	2 L	0.8 L
Capacity	Max	4 L	1.6 L
MOC		Contact Parts: SS 316 Non- Contact parts: SS 304	
Power Supply		415 V, 3 Phase, 50 Hz	

Saizoner Rapid Mixer Granulator

Intragranular	% in formula	mg / Tablet
Intragranular Excipients		
Metformin Hydrochloride	48.31	500
Compritol 888 ATO	38	393.3
Plasdone™ K 29/32	5	51.75
Avicel® PH 101	4.94	51.129
Extragranular Excipients		
Prosolv® SMCC 90 HD	3	31.05
Syloid® 244 FP	0.25	2.5875
Magnesium Stearate	0.5	5.175
Total Tablet weight (mg)		**1035**

Wet Non – Aqueous Granulation Process

Intragranular	% in formula	mg / Tablet
Intragranular Excipients		
Metformin Hydrochloride	52.63	500
Compritol 888 ATO	35	332.5
Plasdone™ K 29/32	3	28.5
Avicel® PH 101	5.26	49.97
Extragranular Excipients		
Prosolv® SMCC 90 HD	3.43	32.585
Syloid® 244 FP	0.25	2.375
Magnesium Stearate	0.5	4.75
Total Tablet weight (mg)		**950**

Granulating Solvent: Methylene Chloride

Evaluation

Physical Characterization	• Bulk density, Tap density & Flow properties of granules using Electrolab Densitometer • Avg. weight, Hardness and thickness of tablets.
Dissolution Studies	• Test 1 & 2 • Apparatus: 2 (Paddle Type) • Phosphate buffer, pH 6.8, 1000 ml • 100 rpm • Time points: 1, 2, 3, 6 & 10 hours
Differential Scanning Calorimetric, DSC	• Heat rate: 35°C to 300°C @ 10°C / min. • Pyris 6, Perkin Elmer.
Scanning Electron Microscopy	• Performed using JSM-5200 (JEOL, Japan) operated at 20 KV with Platinum sputtering for 20 sec • samples mounted on carbon tape
Content of Methylene Chloride by Gas Chromatography	• USP 467 monograph on Residual solvents as specified in USP 32/ NF 27 • Identification, quantification & control of Class 2 Residual solvent in water soluble substances (Procedure C) by head space analysis.

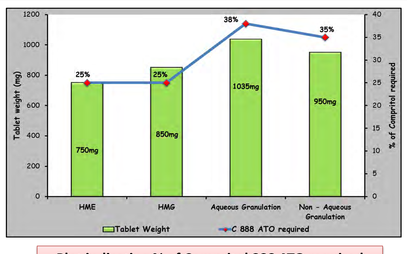
RESULTS AND DISCUSSION

Physical Characterisation

USP Specification			Observation				
Compressibility Index (%)	Flow Characteristics	Hausner Ratio		HME	HMG	Aqueous	Non - aqueous
< 10	Excellent	1.00 - 1.11	Bulk Density (g/ml)	0.513	0.57	0.41	0.4
11 - 15	Good	1.12 - 1.18	Tap Density (g/ml)	0.645	0.80	0.51	0.65
16 - 20	Fair	1.19 - 1.25	Compressibility Index (%)	20.51	28.57	20.41	38.00
21 - 25	Passable	1.26 - 1.34	Hausners ratio	1.258	1.4	1.26	1.61
26 - 31	Poor	1.35 - 1.45					
32 - 37	Very Poor	1.46 - 1.59					
> 38	Very very Poor	> 1.60					

- ✓ Granules prepared using HME process showed appreciable flow & compaction properties
- ✓ Granules prepared using Non – Aqueous granulation processes exhibited poor flow and compression properties with prominent tablet defects.
- ✓ Flow properties of granules prepared using HMG & aqueous granulation processes were passable and afforded good tablets after addition of extragranular material like MCC & Silicon dioxide.

Tablet Parameters	HME	HMG	Aqueous	Non – aqueous
Description	White, Oval shaped tablets	White, Oval shaped tablets	White, Capsule shaped tablets (Caplets)	White, Capsule shaped tablets (Caplets)
Dimensions	Length: 16 mm Width: 9 mm Thickness: 7 mm	Length: 16 mm Width: 9 mm Thickness: 8 mm	Length: 19 mm Width: 9 mm Thickness: 6.8 mm	Length: 19 mm Width: 9 mm Thickness: 5.95 mm
Hardness range (Avg.10 tablets)	80 – 120 N	80 – 120 N	134.9 – 142.5 N	100 – 120 N



Plot indicating % of Compritol 888 ATO required and its impact on Tablet weight

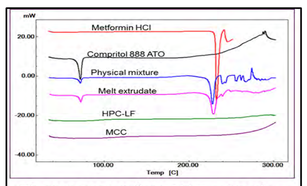
Melt processes:

- ✓ Desired release profile achieved at 25% Compritol 888 ATO levels in formulation.
- ✓ Optimized formulation with low tablet weight: 750 mg for HME & 850 mg for HMG.
- ✓ Minimum extragranular excipients required to achieve desired release profile

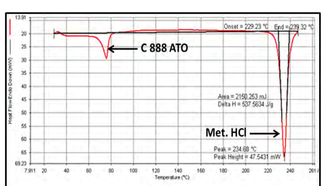
Wet Granulation processes:

- ✓ Desired release profile achieved at 38% Compritol 888 ATO levels for aqueous granulation & at 35% for Non - aqueous granulation .
- ✓ Higher tablet weights in comparison to melt processes.

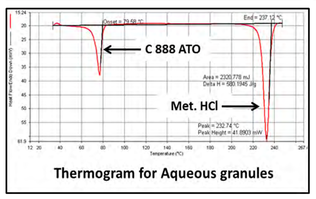
Differential Scanning Calorimetry



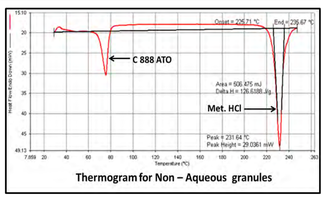
Thermogram for HME extrudes



Thermogram for HMG



Thermogram for Aqueous granules



Thermogram for Non – Aqueous granules

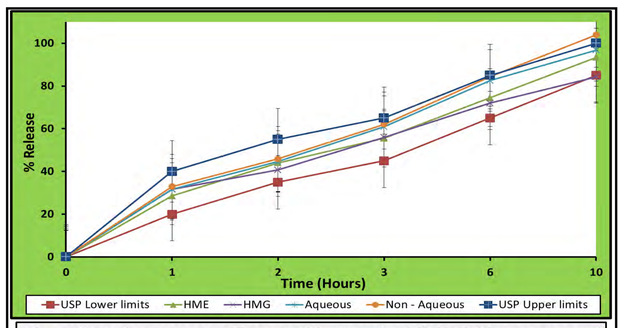
- ✓ Hot melt processes viz. extrusion & granulation resulted in formation of partial solid dispersion of Metformin with Compritol 888 ATO as a decrease in endotherm for Compritol is observed in both processes.
- ✓ No change in the endotherms of Metformin HCl & Compritol 888 ATO were observed in case of aqueous & non aqueous granulation processes indicating formation of physical mixture bound by Polyvinly pyrrolidone as binder.

Content of Methylene Chloride by Gas Chromatography

Class of Solvent	Concentration Limit as per USP 32 / NF 27	Observed Value
Class 2	600 ppm	486 ppm

- ✓ The content of Methylene Chloride in the dried granules prepared using DCM as solvent was well within specification.

Dissolution Studies

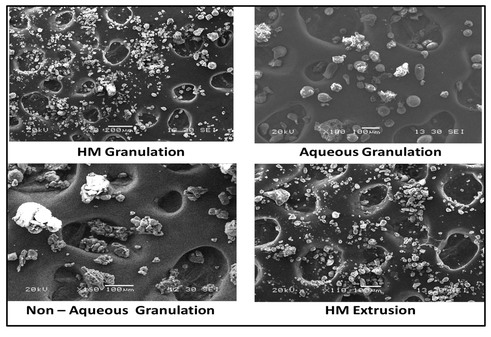


Plot of % Release versus Time for Metformin HCl SR Tablets prepared using HME, HMG, Aqueous and Non – Aqueous granulation process

Time (Hours)	Amount Dissolved (500 mg)
1	20 - 40 %
2	35 - 55 %
3	45 - 65 %
6	65 - 85 %
10	NLT 85 %

Dissolution profiles of Metformin HCl Extended Release tablets, 500 mg prepared using Hot Melt Extrusion, Hot Melt Granulation, Aqueous Granulation and Non Aqueous Granulation techniques complies with the specifications of Test 1 & 2 for dissolution of Metformin HCl Extended Release tablets, USP 37 / NF 32.

Scanning Electron Microscopy



- ✓ In case of Hot melt processes intimate mixing of Metformin HCl and Compritol® 888 ATO is observed resulting in formation of partial solid dispersion.
- ✓ Stability of partial solid dispersion can be attributed to the addition of Hydroxy Propyl Cellulose (Klucel LF) as meltable binder.
- ✓ In case of aqueous & non – aqueous wet granulation processes Metformin HCl & Compritol® 888 ATO co – exist as physical mixture bound together by Polyvinly pyrrolidone (Plasdone® K 29/32) as binder.

Summary

- ✓ Hydroxy Propyl Cellulose (Klucel LF) as meltable binder proved effective in Hot Melt processes (HME & HMG) while Polyvinyl Pyrrolidone (Plasdone™ K29 /30) proved effective as binder for wet granulation processes (Aqueous & Non – aqueous).
- ✓ Flow properties of the granules can be graded as: HME > HMG ≡ Aqueous granulation > Non – Aqueous granulation.
- ✓ Tablet weights of Metformin HCl Extended Release tablets, 500 mg were observed to be: HME (750 mg) < HMG (850 mg) < Non – aqueous granulation (950 mg) < Aqueous granulation (1035 mg).
- ✓ Hot melt processes resulted in slight fusion of Metformin HCl and Compritol® 888 leading to formation of partial solid dispersion with the aid of Klucel LF, while aqueous & non – aqueous wet granulation processes Metformin HCl & Compritol® 888 ATO co – exist as physical mixture bound together by Polyvinly pyrrolidone (Plasdone™ K 29/32) as binder.
- ✓ Optimized formulations prepared using the four granulation techniques gave tablets that complied with dissolution Test 1 & 2 specified in the USP 37/ NF 32 monograph for Metformin HCl Extended Release Tablets, 500 mg.

Conclusion

Amongst the four granulation processes evaluated the melt processes provided Metformin HCl Extended release tablets USP/NF, 500 mg with low tablet weight, lesser quantity of excipients and ease of processability.

Acknowledgement

The presenters would like to acknowledge Ashland Inc., Evonik India Pvt. Ltd., JRS Pharma, Grace Davison Chemical India Pvt Ltd. for the generous gift samples

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M 1160 Development of sustained release ibuprofen capsules by continuous melt granulation-extrusion

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KEY POINTS

Dosage form: 300mg sustained release ibuprofen granules (in capsule)

Process: Continuous melt granulation with 90% drug and 10% Compritol 888

Interest: Low temperature granulation without downstream processing

Findings: Granulation temperature profile and dissolution apparatus are important

New insights: The addition of Gelucire 48/16 optimizes drug release

INTRODUCTION

Ibuprofen is a slightly soluble drug with a short half-life. Formulation into sustained release dosage forms is of interest to maintain therapeutic plasma concentrations over a prolonged period[1]. Twin screw extrusion is an interesting manufacturing option for modified release dosage forms. This study demonstrates the utility of Compritol 888 (a behenic acid glyceride ester) in a plasticizer-free, low temperature continuous extrusion process to produce extended release formulations. The extruder was modified to enable the production of granules directly thereby avoiding the need for downstream processing of extrudate strands.

EXPERIMENTAL METHODS

A formulation of 90% ibuprofen and 10% Compritol 888 was pre-blended in a Turbula and processed using a Pharma 11 HME twin screw extruder (Thermo Fisher). The die plate was removed for granule production. The granulation temperature was reduced from feed to die. Throughput was 200g/h and screw speed 150rpm. Drug release was measured with the USP I and II apparatus (Sotax AT7) in 900mL buffer medium pH 6.0 at 30rpm, 37°C and 263nm. 0.5% Ac-Di-Sol or 2% Gelucire 48/16 were alternatively added to the blend prior to continuous melt granulation.

CONCLUSION

300mg sustained release ibuprofen granules were successfully produced by continuous melt granulation using an extruder with only 10% Compritol 888 ATO. Particle size could be modified by adjusting the granulation temperature. Drug release was extended to 12h and could be easily adjusted to the desired target by adding small concentrations of a disintegrating agent (Ac-Di-Sol) or water soluble surfactant (Gelucire 48/16). In dissolution testing, the paddle apparatus (USP II) gave different release kinetics than the basket (USP I).

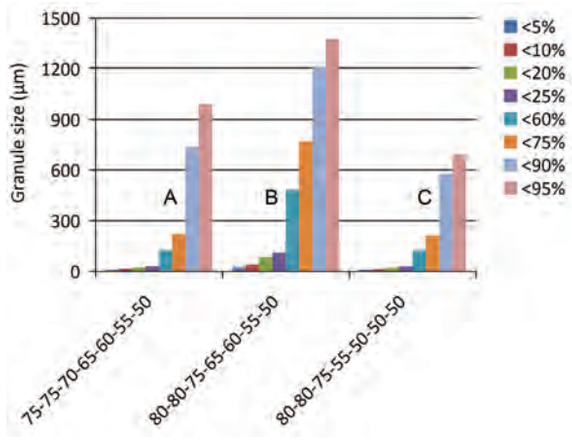
RESULTS AND DISCUSSION

Continuous melt granulation with 90% drug reduces product size and production time

A formulation of ibuprofen: Compritol 888 (ratio 9:1) was successfully extruded through a 1mm die. However size reduction to granules was required to produce the final dosage form.

Removal of the die enabled granule production directly from the extruder avoiding the need for additional processing.

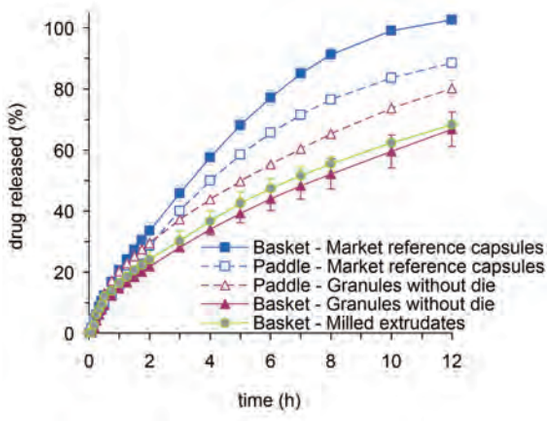
Temperature profile defines granule size



The barrel temperature was set to 75°C in the first two barrel sections to enable the melting of Compritol 888 and homogeneous mixing with ibuprofen. The temperature was then gradually decreased to 50°C prior to the exit to enable lipid crystallization and granule formation (Profile A).

Different temperature set-up resulted in different granule sizes (Profile B and C).

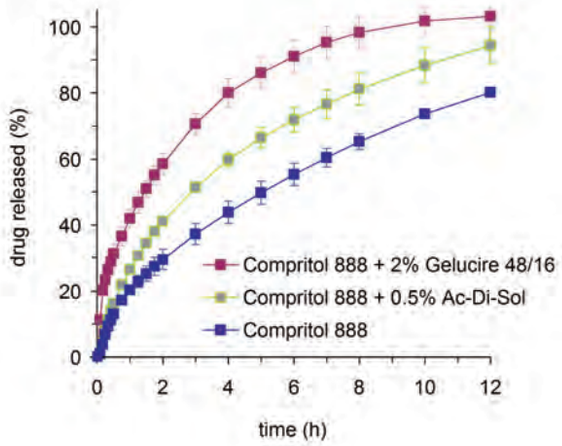
The choice of dissolution apparatus matters



Capsules filled with granules from temperature profile C released the drug similarly to granules obtained by melt extrusion and subsequent milling (red triangle vs green circle). However, **drug release from Compritol 888 granules was 35.9% less than was released from the market reference capsules when the baskets were used** (red triangles vs blue squares).

Replacement of the baskets by **the paddles reduced the release kinetics to 88.5 ± 1.7% for the market reference and increased the release rate to 80.2 ± 2.7% for the Compritol 888 granules** (open squares vs open triangles), providing similar release profiles. This was likely due to floating of the reference capsules on the top of the release medium and improved wetting of the Compritol 888 granules without the basket.

Drug release kinetics can easily be adjusted



Incorporating 0.5% Ac-Di-Sol or 2% Gelucire 48/16 into the formulation prior to continuous granulation increased the release kinetics to 94.4 ± 1.3% and 103.2 ± 4.2% respectively.

Ac-Di-Sol enabled granule disintegration, the addition of the water soluble surfactant Gelucire 48/16 provided improved wetting and subsequent micelle formation, leading to accelerated and complete drug release.

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M 1161

New insights into the stability of SR lipid matrix tablets

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KEY POINTS

Dosage form: 100mg sustained release theophylline tablets

Process: Direct compression

Interest: Novel technique to investigate drug release instability in intact SR lipid matrix tablets

Findings: Compritol 888 polymorphism is not responsible for drug release instability

New insights: Physico-chemical properties of diluents may impact drug release stability

INTRODUCTION

Solid lipid excipients are crystalline materials which exhibit different polymorphs[1]. Used as sustained release (SR) matrix formers, the lipid crystal lattice and inherent polymorphs can change over time, potentially affecting the release kinetics of oral solid dosage forms *in vitro*. Lipid polymorphism is therefore the most widely reported reason for storage instability of SR solid lipid dosage forms[2]. To our knowledge however, no direct correlation between polymorphic evolution of the lipid excipient and drug release has been established. Given numerous functional advantages of solid lipid excipients it is worthwhile investigating the real impact of lipid polymorphism on drug release stability using new techniques such as micro x-ray diffraction. This method enabled the first time analysis of the polymorphic state of Compritol 888 within intact tablets before and after storage, and the correlation of the lipid polymorph with the respective drug release kinetics.

EXPERIMENTAL METHODS

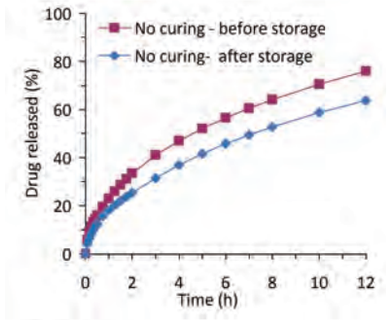
20% theophylline, 15% glyceryl behenate (Compritol® 888 ATO), 32.25% DCPA (Fujicalin SG), 32.25% lactose (Tablettose 80) and 0.5% magnesium stearate was compressed into 12mm flat tablets using a RIVA Piccola rotary press at 30rpm and 18kN. Tablets (uncured and cured for 7 days at 50°C) were stored in closed glass vials at 40°C/75% RH. The Compritol 888 polymorph was determined by micro X-ray diffraction as described by Jannin et al.[3].

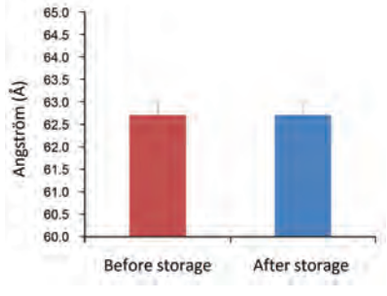
CONCLUSION

Drug release changes after storage with solid lipid SR matrix tablets were not related to evolution of the lipid polymorph. The present study casts doubt on the widely reported theory that lipid polymorphism affects drug release over time. New hypothesis are warranted including the sensitivity of certain tablet ingredients to moisture.

RESULTS AND DISCUSSION

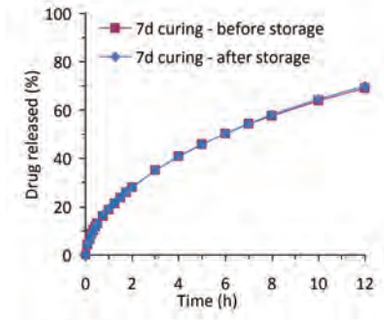
Drug release changes are not related to Compritol 888 polymorphism

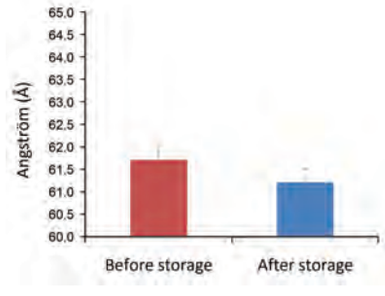




Micro X-ray diffraction allowed elucidation of the actual polymorphic state of Compritol 888 in a tablet formulation and correlation of the lipid polymorph with the drug release kinetics. **Drug release from uncured tablets decreased after 45 days of storage although no changes in the polymorph of Compritol 888 were observed.**

Tablet curing enables stable drug release although the polymorph changes





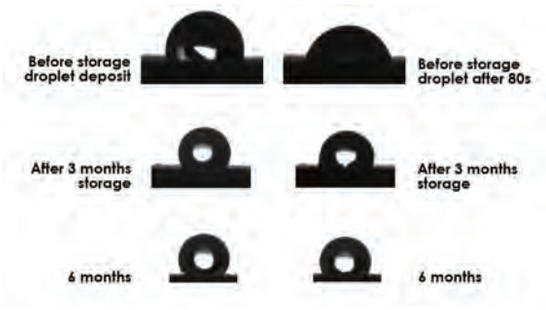
The polymorph of Compritol 888 in cured tablets changed during storage (although insignificantly from 61.7 to 61.2Å) whilst drug release was stable (f2 = 98.4). Within the scope of this study we demonstrate that an **evolution of the lipid polymorph is not necessarily linked to drug release changes over time.**

Tablet physicochemical properties do not affect drug release stability

Tablet	Weight (mg)	Thickness (mm)	Tensile strength (MPa)
No curing - before storage	503 ± 4.1	3.23 ± 0.02	1.55 ± 0.08
No curing - after storage	503 ± 3.6	3.24 ± 0.03	1.45 ± 0.09
7d curing - before storage	504 ± 4.0	3.25 ± 0.02	1.21 ± 0.06
7d curing - after storage	504 ± 4.5	3.22 ± 0.03	1.38 ± 0.04

Several hypotheses can be envisaged to explain the observed changes of drug release kinetics from uncured tablets after storage: (i) evolution of the physicochemical properties of the tablet, (ii) changes in matrix porosity or (iii) wettability of the tablets. 45 days of storage slightly reduced the crushing strength of uncured tablets, but increased the strength of cured tablets. Drug release variations however could not be related to these differences. **Tablet weight and thickness remained unchanged during storage and did therefore not affect drug release.**

Diluents type and humidity might induce drug release changes



Excipient	f2 at 40°C	f2 at 40°C/75% RH
Fujicalin SG	86	51
Emcompress anhydrous	66	66
Emcompress Premium	87	80

The matrix wettability was reduced after storage which can slow down water diffusion into the tablet and drug diffusion out of the tablet, resulting in slower drug release kinetics. A change of wettability can have different causes: humidity during storage (75% RH) can induce moisture saturation resulting in reduced wettability of the uncured tablets after storage. Interestingly this effect was reduced or even absent when Fujicalin was replaced by the chemically identical excipient Emcompress. **The physical nature of the filler may impact release rate changes over time rather than the lipid polymorph.**

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[3] Jannin, V. *et al.* J. Control. Rel. 197 (2015) 158–164

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NEW INSIGHTS INTO THE STABILITY OF SR LIPID MATRIX TABLETS

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1 - ABSTRACT

Lipid polymorphism is the most widely reported theory for the instability of drug release after the storage of solid lipid dosage forms. The present work gives new insights into the real-time polymorphic changes of Compritol 888 in tablets prepared by direct compression. A non-destructive analytical method was used allowing correlation of the type of lipid polymorph with the respective drug release kinetics prior to and following storage at 40°C. The findings indicate a new theory behind the sometimes encountered changes in drug release profile during storage.

2 - INTRODUCTION

Solid lipid excipients are crystalline materials which exhibit different polymorphs[1]. Used as sustained release (SR) matrix formers, the lipid crystal lattice and inherent polymorphs can change over time, potentially affecting the release kinetics of oral solid dosage forms *in vitro*. Lipid polymorphism is therefore the most widely reported reason for storage instability of SR solid lipid dosage forms[2]. To our knowledge however, no direct correlation between polymorphic evolution of the lipid excipient and drug release has been reported yet.
Given numerous functional advantages of solid lipid excipients it is worthwhile investigating the real impact of lipid polymorphism on drug release stability using new techniques such as micro x-ray diffraction. This method enabled analysis of the polymorphic state of Compritol 888 within intact tablets before and after storage, and the correlation of the lipid polymorph with the respective drug release kinetics for the first time.

3 - EXPERIMENTAL METHODS

20% theophylline, 15% glyceryl behenate (Compritol® 888 ATO), 32.25% DCPA (Fujicalin SG), 32.25% lactose (Tablettose 80) and 0.5% magnesium stearate was compressed into 12mm flat tablets using a RIVA Piccola rotary press at 30rpm and 18kN. Tablets (uncured and cured for 7 days at 50°C) were stored in closed glass vials at 40°C/75% RH. The Compritol 888 polymorph was determined by micro X-ray diffraction. The exact set-up is described by Jannin et al.[3]

4 - RESULTS AND DISCUSSION

Micro X-ray diffraction allowed elucidation of the actual polymorphic state of Compritol 888 in a tablet formulation and correlation of the lipid polymorph with the drug release kinetics. The bars on the x-axes in Figure 1 represent the diffraction peaks of Compritol 888 (polymorph) before and after 45 days of storage for uncured and cured tablets. The respective release profiles are shown below.

Drug release from uncured tablets decreased after 45 days of storage although no changes in the polymorph of Compritol 888 were observed (blue bars). In contrast, the polymorph of Compritol 888 in cured tablets changed (although insignificantly, red bars) whilst drug release after storage was stable.

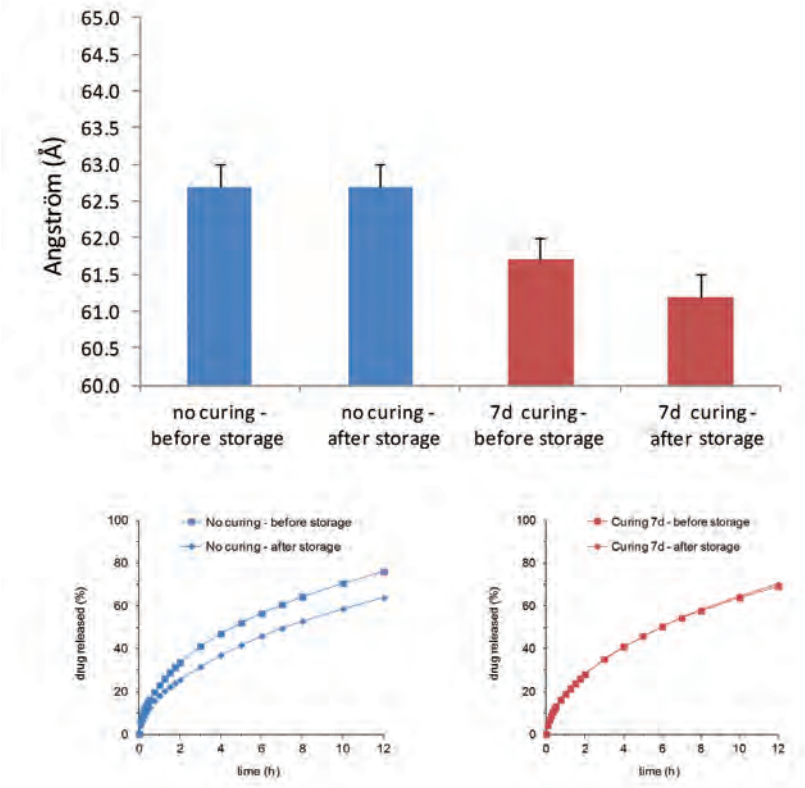

Figure 1: Correlation of the real-time polymorphic state of Compritol 888 with the drug release kinetics before and after 45 days storage.

Within the scope of this study we demonstrate that an evolution of the lipid polymorph is not necessarily linked to drug release changes over time.

Therefore several hypotheses can be envisaged to explain the observed changes of drug release kinetics after storage, including: (i) evolution of the physicochemical properties of the tablet, (ii) changes in matrix porosity or (iii) wettability of the tablets.

Table 1 summarizes the physicochemical properties of the tablets before and after storage for 45 days. The crushing strength slightly decreased for uncured tablets, and increased for the cured tablets. Nevertheless, the differences in tablet hardness could not be correlated to drug release variations (data not shown). Tablet weight and thickness remained unchanged during storage and do therefore not affect drug release (Table 1).

Table 1: Physicochemical tablet properties.

Tablet	Weight (mg)	Thickness (mm)	Tensile strength (MPa)
No curing - before storage	503 ± 4.1	3.23 ± 0.02	1.55 ± 0.08
No curing - after storage	503 ± 3.6	3.24 ± 0.03	1.45 ± 0.09
7d curing - before storage	504 ± 4.0	3.25 ± 0.02	1.21 ± 0.06
7d curing - after storage	504 ± 4.5	3.22 ± 0.03	1.38 ± 0.04

Figure 2 shows the evolution of the contact angle of a water droplet onto the tablet surface during storage for 3 months. It is clear that the wettability of the matrix is reduced after storage which can lead to the deceleration of water diffusion into the tablet and drug diffusion out of the tablet, therefore leading to slower drug release kinetics. The change of wettability can have different causes. For instance, humidity during storage (75% RH) can induce moisture saturation leading to reduced matrix wettability (Table 2).

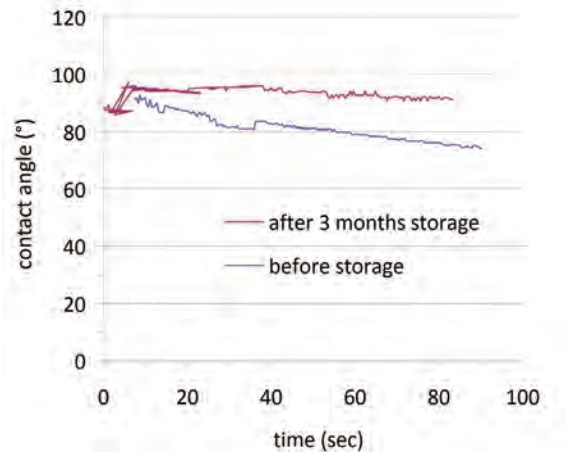

Figure 2: Wettability of the uncured tablets before and after 3 months storage.

Table 2 illustrates how the presence of humidity during storage can impact drug release from the investigated tablets. The similarity factor f2 decreased from 86 to 51 at 75% RH for the uncured tablets (Fujicalin), indicating a difference of almost 10% between the release kinetics before and after 6 months storage. Interestingly this effect was reduced or even absent when Fujicalin was replaced by the chemically identical excipient Emcompress (Table 2). The physical nature of the filler might therefore be a determining factor in release rate changes over time rather than the lipid polymorph.

Table 2: Effect of humidity on drug release after 6 months storage.

Excipient	Chemical	f2 at 40°C	f2 at 40°C/75% RH
Fujicalin SG	DCPA*	86	51
Emcompress anhydrous	DCPA	66	66
Emcompress Premium	DCP*	87	80

* DCP(A) = Dibasic calcium phosphate (anhydrous)

5 - CONCLUSION

Drug release changes after storage with solid lipid SR matrix tablets were not related to evolution of the lipid polymorph. The present study casts doubt on the widely reported theory that lipid polymorphism affects drug release over time. New hypothesis are warranted including the sensitivity of certain tablet ingredients to moisture. Further investigations will follow.

6 - REFERENCES

[1] Sato, K. Chem. Eng. Sci. 56 (2001) 2255-2265.
[2] Windbergs, M. et al. Eur. J. Pharm. Biopharm. 71 (2009) 80–87.
[3] Jannin, V. et al. J. Control. Rel. 197 (2015) 158–164.

Yvonne Rosiaux

W5168

ETHANOL RESISTANT EXTENDED RELEASE MATRIX TABLETS WITH COMPRITOL® 888 ATO

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INTRODUCTION

Accidental dose dumping induced by the concomitant intake of alcoholic beverages with a drug product is mainly linked to the uncontrolled dissolution of the functional excipient in ethanol[1,2]. Dose dumping becomes a serious safety concern with extended release products, which contain higher drug concentrations compared to immediate release dosage forms. Compritol® 888 ATO is a lipid matrix agent used in sustained release tablets. It is insoluble in ethanol and exhibits interesting features to prevent alcohol related dose dumping.

EXPERIMENTAL METHODS

Compritol® 888 ATO (glyceryl behenate NF), drug and excipients (Table 1) were blended using a Turbula at 90 rpm for 10 min. The powder blend was lubricated with magnesium stearate at 90 rpm for 1 min prior to compression with flat tooling at 18 kN. 100 mg theophylline tablets were obtained using a single station press (Korsch EK0, 333 mg total weight, 10 mm diameter). 500 mg niacin tablets were prepared with a multi station press (Riva Piccola, 1000 mg total weight, 12 mm diameter). Drug release from tablets was measured in 0.1N HCl and 0.1N HCl: 40% ethanol for 2h at 37°C (Sotax AT7), referring to the FDA worst case guidance. Similarity of drug release in both media was concluded when $50 \leq f2 \leq 100$. The wettability of tablets was quantified by measuring the contact angle of 0.1N HCl and 0.1N HCl: 40% ethanol to the tablet surface. 15 µL of liquid was dropped onto the flat tablet surface using a goniometer (R GBX 01) equipped with a Nikon camera. The mean value of the left and the right contact angle was calculated.

Table 1: Composition of sustained release matrix tablets.

Ingredients, % w/w	Formulation F1	Formulation F2	Formulation F3	Formulation F4
Theophylline	30	30	-	-
Niacin	-	-	63	63
Compritol® 888 ATO	19.5	19.5	20	20
Avicel PH101 (MCC)	50	-	-	-
Flowlac 100 (lactose)	-	50	-	-
Emcompress (DCP)	-	-	15	-
Ethocel 10 FP (EC)			-	15
Aerosil Pharma 200			1.5	1.5
Magnesium stearate	0.5	0.5	0.5	0.5

RESULTS AND DISCUSSION

Compritol® 888 ATO does not dissolve in water or ethanol. Excipient-related dose dumping in hydro-alcoholic media is therefore absent. However, the solubility of the drug can significantly change. Since drug release from Compritol® 888 tablets is driven by diffusion this change in drug solubility will likely affect the release kinetics.

Figure 1 shows the effect of hydro-alcoholic media on theophylline solubility and the consequence on tablet wettability and drug release from Compritol® 888 tablets containing MCC as filler (F1). Theophylline is threefold more soluble in 40% ethanol compared to 0.1N HCl (Figure 1a). This results in improved tablet wetting (Figure 1b). Consequently theophylline release is faster in 0.1N HCl: 40% ethanol than in 0.1N HCl ($f2 = 33.5$, Figure 1c). Such undesired rapid drug release in hydro-alcoholic fluid can be prevented by using a filler that is less soluble in ethanol than in HCl: e.g. lactose. When replacing MCC by lactose (F2), tablet wetting in 40% ethanol is reduced and is more similar to the tablet wettability in 0.1N HCl (Figure 1d). Theophylline release in the presence of lactose is hence unaffected in both media with $f2 = 73.5$ although drug solubility is threefold increased (Figure 1e).

The opposite occurs with niacin (vitamin B3) which exhibits twofold less solubility in 0.1N HCl: 40% ethanol compared with 0.1N HCl (Figure 2a). This results in slower release kinetics when DCP is the filler ($f2 = 37$, Figure 2b). Similar to the first part of this study 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 2c).

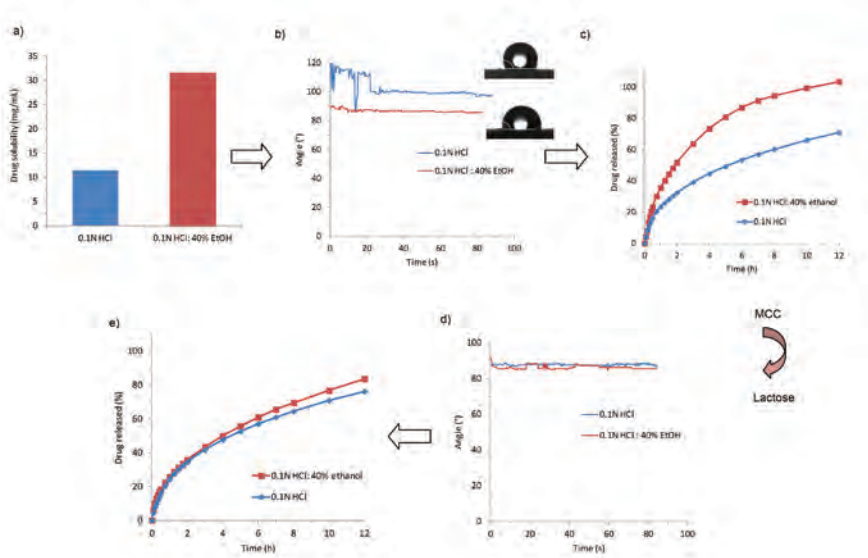

Figure 1: Effect of drug solubility on matrix wettability and drug release kinetics in 0.1N HCl and 0.1N HCl: 40% ethanol from tablets produced by direct compression with Compritol® 888 ATO, MCC (F1) and lactose (F2).

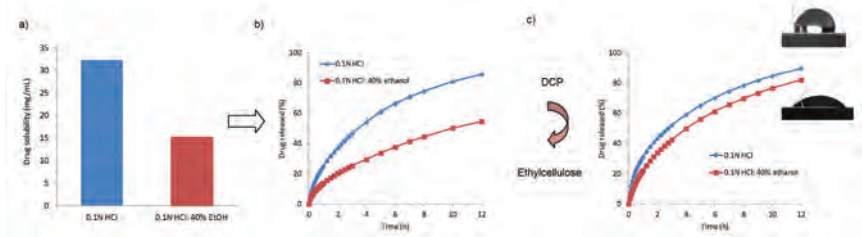

Figure 2: Effect of hydro-alcoholic media on: a) niacin solubility, b) niacin release from Compritol® 888: DCP tablets (F3) and c) niacin release from Compritol® 888: ethylcellulose tablets (F4).

CONCLUSION

For certain drug compounds the prevention of alcohol related dose dumping is pre-requisite. This needs to be addressed during the formulation stage of drug development. More and more compounds are coming under scrutiny and application of the FDA guidelines for testing for resistance to alcohol should be considered during drug development. The use of Compritol® 888 ATO with appropriate diluents provides a practical and robust solution for the formulation of drugs whose solubility hence dissolution from extended release tablets can be affected by alcohol.

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ESTIMATING *IN VIVO* DRUG RELEASE FROM A NEW THEOPHYLLINE COMPRITOL® 888 ATO MATRIX FORMULATION USING APPROPRIATE BIORELEVANT TEST METHODS

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1 - INTRODUCTION

Oral extended-release (ER) dosage forms have represented a broad segment of research and development in the pharmaceutical industry for many years. Housing drugs with a short half-life they can typically enable a reduced dosing frequency which comes along with various potential advantages such as e.g. reduced fluctuations in drug levels, a reduced total amount of drug that has to be used, improved patient compliance, better and more uniform clinical effects, lower incidence of side effects.

Since drug absorption from ER dosage forms is governed by the rate of release from the formulation and since these formulations typically contain much higher drug doses than the respective immediate-release (IR) formulations, it is essential to assure robust and reproducible *in vivo* drug release to prevent the unwanted toxic peaks and sub-therapeutic troughs in plasma levels caused by "dose dumping" or insufficient/hindered drug release.

Matrix-based formulations, consisting of the active drug embedded in a polymer matrix which controls drug release, have traditionally been the most commonly used ER dosage forms. Traditionally, a whole range of water-soluble or water-swellabe polymers with high molecular weight with HPMC being the most representative candidate have been used as matrix formers. However, some of these formulations have shown increased sensitivity to the composition of gastrointestinal fluids and gastrointestinal shear forces [1-2] which could not be predicted by standard dissolution experiments in the paddle or basket apparatus.

To predict whether the ER dosage form meets its *in vivo* release profile goals, one needs to apply an adequate release test system that reflects conditions relevant to the *in vivo* conditions of drug release.

The aim of the present set of experiments was evaluate the robustness of lipid based theophylline matrix tablets in various biorelevant dissolution test devices simulating passage through the human gastrointestinal (GI) tract. Compritol® 888 ATO (glyceryl dibehenate, NF), the matrix former, is a fine white powder composed of spherical particles with a mean particle diameter of 50µm. It has excellent tabletting properties and is chemically inert and neutral in flavor. With a low HLB of 1 and a high melting point (70°C) it has proven utility in the production of an insoluble and non-swellable matrix which sustains drug release principally by a mechanism of diffusion.

2 - EXPERIMENTAL METHODS

Theostat® L.P. 100 mg, lot # G00405 (Pierre Fabre Medicament, Boulogne, France) was obtained by prescription, Theophylline, Compritol® 888 ATO, dicalcium phosphate anhydrate (DCPA, Fujicalin®), lactose monohydrate, silicon dioxide (Aerosil® 200), Mg alumino metasilicate (Neusilin® US2) and magnesium stearate used for manufacturing the tablets as well as sodium chloride, hydrochloric acid conc., sodium dihydrogen phosphate, sodium hydroxide and acetic acid used to prepare the release media were all of analytical grade and purchased commercially.

100 mg theophylline, Compritol® 888 ATO and diluents were sieved through a 810 µm mesh, blended, subsequently lubricated and compressed using a single punch excenter press (14 mm, Korsch EK03). The total tablet weight was 600 mg.

Table 1: Composition of theophylline matrix tablets containing Compritol® 888 ATO.

Ingredient	%
Theophylline	16.7
Compritol® 888 ATO	15.0
DCPA (Fujicalin® SG)	42.9
Lactose	21.4
AL_2O_3-MgO-SiO_2 (Neusilin® US2)	3.0
Magnesium stearate	1.0

Table 2: Dissolution media [3] and corresponding residence times.

GI section	Medium	pH	Residence
Stomach	SGF / FaSSGF	1.8	60 min
Small intestine	(Blank) FaSSIF	6.8	240 min
Proximal colon	SCoF	5.8	240 min
Colon	Blank FaSSIF	6.5	180 min

Dissolution studies were performed at 37°C with a) the reciprocating cylinder apparatus, (USP III; ERWEKA RRT 10: 200 mL per vessel, 420 µm mesh screens, 10 dpm), b) the flow through apparatus (USP IV; ERWEKA DFZ: 22.6 mm cell filled with 1 mm-size glass beads, Whatman® glass fiber filter (GF/F), tablets on holder, flow rates: stomach: 8 mL/min, small intestine and colon: 4 mL/min), and c) an ERWEKA biorelevant dissolution stress test apparatus intended to reflect phases of pressure waves simulating episodes of high gastrointestinal motility (gastric emptying (GE), ileocecal passage (ICP)) and phases of transport (780 mL, 100 rpm, 3 pressure waves (300 mbar) for gastric emptying and ileocecal passage, 1 min rotation at 100 rpm every 10 min for intestinal transport events). Results in USP III and IV were performed in the buffer media, whereas in the stress test experiments both buffers and the corresponding biorelevant media (with bile compounds) were used. Media and corresponding residence times are given in Table 2.

3 - RESULTS & DISCUSSION

Results from the experiments simulating a fasted gastrointestinal passage of monolithic dosage forms show slight differences in the release profile which is most likely due to the nature of the apparatus and the test settings which are likely to result in different hydrodynamic conditions. Overall, both the Theostat® L.P. 100 mg marketed product and the theophylline Compritol® 888 ATO matrix formulation are neither sensitive towards the changing pH-conditions (Figures 1-3), nor are significantly affected by biorelevant gastrointestinal stress conditions in the fasted GI tract (Figures 3 and 4).

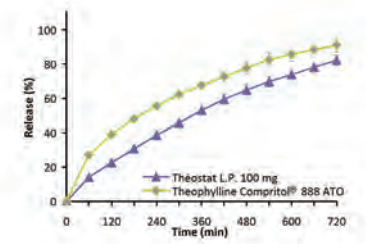

Figure 1: Theophylline release from different tablets under simulated fasted conditions in the reciprocating cylinder apparatus equipped with buffer media (mean of n = 3, ± SD).

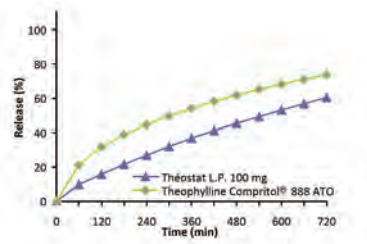

Figure 2: Theophylline release from different tablets under simulated fasted conditions in the flow through apparatus equipped with buffer media (mean of n = 3, ± SD).

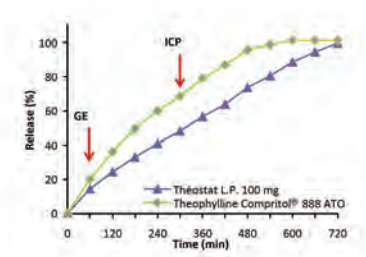

Figure 3: Theophylline release from different tablets under simulated fasted conditions in the biorelevant stress test apparatus equipped with buffer media (mean of n = 3, ± SD).

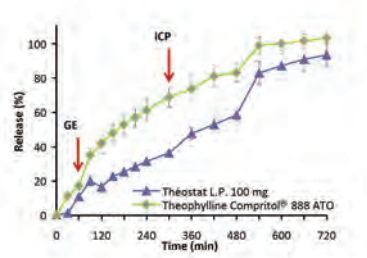

Figure 4: Theophylline release from different tablets under simulated fasted conditions in the biorelevant stress test apparatus equipped with biorelevant media (mean of n = 3, ± SD).

4 - CONCLUSION

Compritol® 888 matrix tablets prepared by direct compression offer a quite robust sustained release in biorelevant fasted conditions even when exposed to simulated mechanical stress in the fasted human GIT. Further studies should be carried out in fed conditions - which exert a significant role in drug dose dumping.

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STREAMLINING THE DESIGN OF SUSTAINED RELEASE MATRIX TABLETS USING MATHEMATICAL MODELING FOR DRUG RELEASE OPTIMIZATION

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1 - INTRODUCTION

During formulation development of a sustained release matrix tablet, it is important to define the optimal concentration of the release retarding matrix agent. The percolation threshold or the minimum amount required to create an infinite matrix network has to be studied to ensure the robustness of the matrix. Evaluation of this critical value helps therefore to implement the principles of QbD into product development.
Compritol® 888 ATO is a glyceryl behenate with low HLB (1) and high melting point (70°C). It is water insoluble and non-swellable. To predict drug release from Compritol® 888 matrices a simplified equation of Fick's law of diffusion can be applied because lipid matrix remains intact during dissolution and drug release[1]. Otherwise geometric changes of the device can induce changes in the drug release mechanism (e.g. erosion).
The release profiles of theophylline tablets made with varying Compritol® 888 concentrations have been semi-empirically predicted based on three initial lipid excipient concentrations. This process can allow a faster drug product development and cost reduction.

2 - EXPERIMENTAL METHODS

Tablet preparation

500 mg tablets contained 20% theophylline, 10-40% Compritol® 888 ATO, qs lactose:dibasic calcium phosphate anhydrous ratio 1:1, 0.5% magnesium stearate. Tablets were prepared by direct compression using a single punch press (Korsch EK0) and 12 mm flat faced tooling at 18kN.

Percolation threshold

The minimum lipid concentration was assessed using a disintegration tester. Tablets were placed into the device and dipped for 120min into 37°C water containing blue dye. Geometric changes of tablets were visually determined.

Drug release modeling/prediction

Theophylline release from tablets was determined using the USP method. Drug is released by diffusion, therefore the simplified Equation 1 of Fick's 2nd law of diffusion has been applied:

$$\frac{M_t}{M_\infty} = 4\cdot\sqrt{\frac{D\cdot t}{\pi\cdot R^2}} - \frac{D\cdot t}{R^2} \qquad \text{Equation 1}$$

where M(t)/M(∞) denotes the cumulative amounts of drug released at time t and infinity respectively, k is the release constant, n is the diffusional exponent, D the diffusion coefficient, R the tablet radius and t the time. D was determined by fitting the model to the experimental drug release profile. This value was then used to semi-empirically predict release kinetics for other drug/lipid concentrations.

3 - RESULTS & DISCUSSION

Tablets containing 10% of Compritol® 888 gradually disintegrated during dipping into 37°C blue colored water in the disintegration tester (Figure 1) indicating the matrix was insufficiently robust. By increasing the lipid amount to 15%, the shape of the tablet remained intact after 120 min of dipping, only minor erosion was seen on the tablet edge. After this rapid screening, 15% of Compritol® 888 was estimated to be the minimum required concentration to create an infinite lipid network with theophylline.

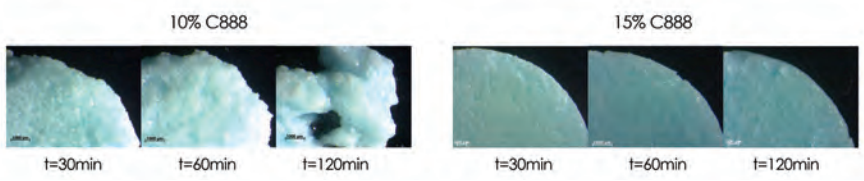
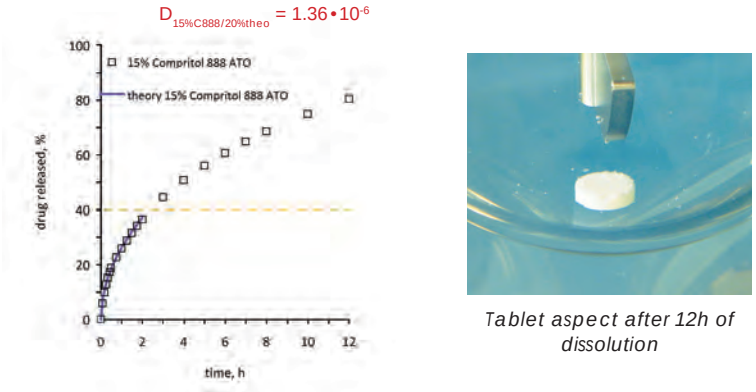


Figure 1: Aspect of tablets containing 10% and 15% of Compritol® 888 after 30, 60 and 120min of dipping into 37°C blue colored phosphate buffer pH4.5.

Drug release from tablets containing 15% of Compritol® 888 and 20% of theophylline is shown in Figure 2 (squares). The drug diffusion coefficient D for theophylline has been determined by fitting the model to the experimental data set using Equation 1 (blue solid line). Note: this simplified model is only valid for up to 40% drug released (orange dotted line).

However, the drug diffusion coefficient D is dependent on the formulation. For prediction it is important to determine other D values for other lipid/drug concentrations. Therefore, tablets with higher lipid (20% and 40% Compritol® 888) and fixed drug concentration were prepared and the respective D values determined as described above. Figure 3 shows the experimental drug release rates, the fitted curves and corresponding D values for 20% and 40% of Compritol® 888.



Tablet aspect after 12h of dissolution

Figure 2: Experimental drug release (squares), D value and modeling (blue solid line) from tablets containing 15% of Compritol® 888 and 20% theophylline.

These known D values could then be correlated to the respective theophylline concentration. Once the best correlation curve is obtained (R^2 close to 1), the D values for other theophylline: Compritol® 888 concentrations can be predicted without any further experiments. These D values can then be used to calculate drug release from tablets with varying Compritol® 888 concentrations using Equation 1, allowing for rapid product optimization. An example is given in Figure 4 where theophylline release has been predicted for 30% of Compritol® 888 (solid curve). These tablets with 30% Compritol have been produced subsequently and released to confirm the predictions from Figure 4. As it can be seen theory (solid curve) and reality (symbols) were in good agreement. Alternatively, the effect of different drug concentrations on release kinetics can be predicted (data not shown).

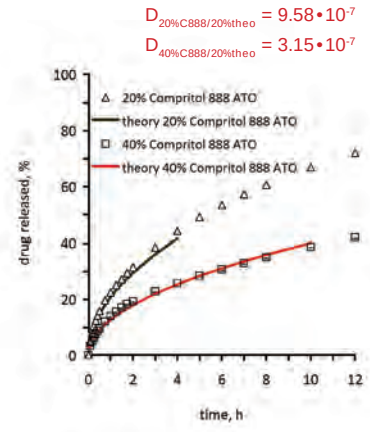


Figure 3: Experimental drug release (symbols), D values and modeling (solid lines) from tablets containing 20% and 40% of Compritol® 888 and 20% theophylline.

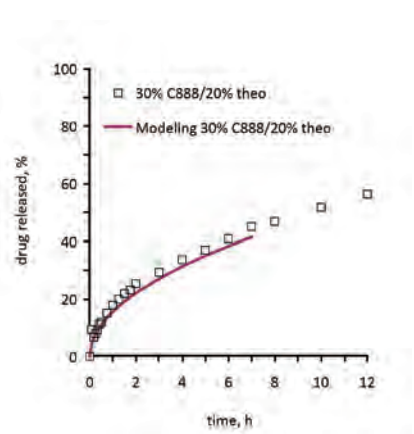


Figure 4: Drug release prediction (solid curves) and independent experimental data sets (symbols) for 30% of Compritol® 888 and 20% theophylline.

4 - CONCLUSION

A rapid screening using a disintegration test enables the minimum amount of Compritol® 888 in theophylline sustained release matrix tablets to be determined. Due to the drug release mechanism being by diffusion only it is possible to predict semi-empirically drug release using Fick's law of diffusion. This can provide time and cost reduction during product development and optimization.

5 - REFERENCES

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THE EFFECT OF THE PROCESS ON DRUG RELEASE OF COMPRITOL® 888 SUSTAINED RELEASE TABLETS: DIRECT COMPRESSION, WET GRANULATION AND HOT MELT EXTRUSION

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1 - INTRODUCTION

Many freely water soluble drug molecules are formulated into sustained release dosage forms in order to reduce daily dosing whilst providing efficacy and safety. However, drug concentrations in sustained release dosage forms are typically high and desired release kinetics can be difficult to achieve.
Compritol® 888 ATO is a glyceryl dibehenate with low HLB (1) and high melting point (70°C) and can therefore be used as sustained release matrix former. Its physicochemical properties as a lipid means it can be formulated in cold as well as in hot processes using a variety of techniques. This provides formulators with a number of different options for achieving the desired drug release kinetics, dosage form performance and manufacturing methods. The present work utilizes three drug molecules with different water solubility that are generally formulated with high doses, and evaluates the impact of formulation process on final tablet properties and drug release profiles. A greater understanding of how different process compare in terms of end-product performance illustrates how selecting the appropriate processing method can simplify and speed-up the formulation development process, reducing development time and costs.

2 - EXPERIMENTAL METHODS

Tablets were prepared by direct compression (DC), wet granulation (WG) and hot melt extrusion (HME) using the model drugs metoprolol succinate (200 mg), nicotinic acid (500 mg) and metformin HCl (500 mg). Tablet compositions are listed in Table 1, tablet weights were 600, 1000 and 1000mg respectively.

Table 1: Tablet formulations (% w/w)

Ingredient	Metoprolol succinate	Nicotinic acid	Metformin HCl
Drug	33.3	50	50
Compritol	40	30	30
Povidone	5	5	5
Lactose	16.7	14.5	-
DCPA	-	-	11
AL_2O_3-MgO-SiO_2	3	-	-
SiO_2	1	-	3
Mg stearate	1	0.5	1

DC: All ingredients were blended in a turbula mixer at 90 rpm for 10min prior lubrication. Tablets were produced using a single punch press (Korsch EK0) with flat faced tooling at 15-18kN. Tablet hardness and friability were measured and tablet tensile strength calculated from tablet height and diameter.
WG: Drug, Compritol® 888 and Povidone were pre-blended in a Turbula mixer and granulated with water using a planetary mixer (Kenwood) at speed level 2. The wet mass was sieved through 2000µm and oven dried overnight prior to dry sieving through 630 µm followed by compression in to tablets, referred to as DC.
HME: Drug and Compritol® 888 were extruded using an 11 mm twin screw extruder (Thermo Fischer). The barrel temperature and screw speed was i) 60-63-68-70-65-70-70-70°C at 100 rpm for metoprolol succinate, ii) 60-63-68-68-65-68-68-68°C at 150 rpm for nicotinic acid and iii) 60-63-68-70-65-70-70-70°C towards the die at 100 rpm for metformin HCl. Feed rate was 200 g/h for all drugs. The 1 mm in diameter extrudates were subsequently milled using an oscillating granulator (630 µm) and compressed into tablets, referred to DC.
Dissolution testing was conducted referred to the respective USP method for each drug molecule.

3 - RESULTS & DISCUSSION

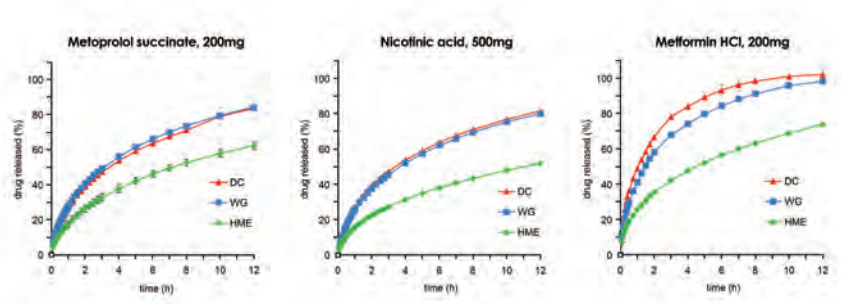

Figure 1: Drug release from tablets containing metoprolol succinate, nicotinic acid and metformin HCl prepared by different processing methods: direct compression (DC), wet granulation (WG) and hot melt extrusion (HME).

For all drugs, sustained release matrix tablets were successfully developed with the different processing techniques. For each drug, differences in tablet properties were observed according to the process used. Tablet tensile strength for example increased in the order of DC<HME<WG whereas friability changed as follows: WG~HME<DC (Table 2).

Table 2: Tablet properties.

	Process	Tensile strength, MPa	Mass uniformity, %	Friability, %
Metoprolol succinate	DC	0.87	0.45	0.85
	WG	1.36	0.49	0.45
	HME	1.13	0.23	0.47
Nicotinic acid	DC	0.73	0.83	1.3
	WG	1.42	0.29	0.6
	HME	1.09	0.25	0.35
Metformin HCl	DC	0.44	0.75	2.12
	WG	1.52	0.33	0.38
	HME	0.9	0.2	0.41

Drug release from these different tablets are shown in Figure 1. Although tablets obtained by WG have the highest hardness, drug release was very similar to tablets made by DC irrespective of the drug type. This is interesting because it means that if the drug development has started with DC, tablet characteristics can be optimized by changing to wet granulation, without changing the drug release profile. On the other hand, for all drugs, the release kinetics was slower when tablets were prepared by HME. This is likely due to the melt process where drug molecules are deeply embedded within the lipid matrix resulting in increased tortuosity, reduced wetting and limited diffusibility of the drug, thereby resulting in slower drug release. Especially for freely soluble drugs or high dose tablets this can be an interesting technique to optimize drug release and tablet size. The ability of Compritol® 888 to be used in many processes is very attracting and presents many advantages. By simply changing the process, product optimization is easier: reformulation can be avoided and process parameters maintained.
All drug release rates were stable (f2>50) after 6 months storage at ambient (25°C/60%RH) and accelerated (40°C/75%RH) conditions (Figure 2).

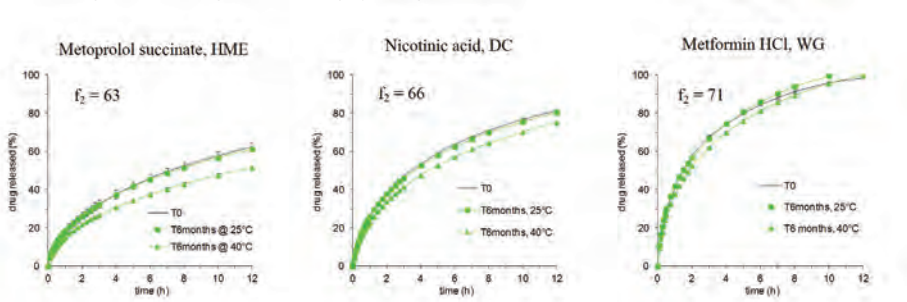

Figure 2: Long term stability of Compritol tablets containing different drugs and produced with different processes.

4 - CONCLUSION

This study compared the impact of process on Compritol® 888 ATO matrix tablets using three different techniques: direct compression, wet granulation and hot melt extrusion. Three water-soluble drugs were used and the same trend was observed when comparing the drug release profiles of tablets having the same composition but made by different processes. The HME technique provided slowest drug release. Matrix tablets prepared by DC and WG show the same release rates, despite a lower tensile strength of tablets made by DC. Tablets providing targeted drug delivery but inconvenient tablet strength can hence be optimized without reformulating by simply changing the process from DC to WG. The initial formulation and compression parameters can thereby be maintained gaining development time. HME or melt processes are interesting to enhance drug retention in the lipid matrix and to reduce high dose drug release.

5 - REFERENCES

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IMPACT OF DILUENT TYPE ON COMPRITOL® 888 ATO SUSTAINED RELEASE TABLETS

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1 - INTRODUCTION

Lipid excipients are widely used in sustained release applications and can be processed by standard techniques such as direct compression and wet granulation or using melt methods. Compritol® is a glyceryl behenate with low HLB (1) and high melting point (70°C) used as a release retarding agent in matrix tablets. The drug release mechanism from Compritol® 888 matrices is diffusion dominated and independent of the processing technique: the drug dissolves and diffuses out of the matrix following water penetration into the dosage form [1]. The creation of pore and water channels controls drug release and these features can be readily used to adjust drug release kinetics. In the present work different types of diluent were evaluated in terms of the impact on pore and water channel formation in order to determine the effect on drug release and long term stability of Compritol® 888 ATO sustained release tablets.

2 - MATERIALS & METHODS

Materials

Theophylline anhydrous (Sigma Aldrich, France); glyceryl behenate (Compritol® 888 ATO, Gattefossé, France); Avicel PH200/PH101 (MCC; FMC, USA); Vivapur 102 (MCC; JRS, Germany); Prosolv SMCC HD90 (silicified MCC; JRS), Emcompress anhydrous/dihydrate (DCPA/DCP; JRS); Fujicalin SG (DCPA; Fuji Chemical, Japan), Lactopress spray dired 202 (lactose; Borculo Domo, Netherlands); Flowlac 100 (lactose; Meggle, Germany); Tablettose 80 (lactose, Meggle); MicroceLac 100 (co-processed lactose-MCC, Meggle), Starlac (co-processed lactose-maize starch, Roquette, France); maize starch (Roquette), CompriO (sucrose, Suedzucker, Germany); magnesium stearate (Sigma Aldrich).

Direct compression

Theophylline (30%), Compritol® (19.5%) and the respective diluents (50%) were blended in a Turbula® mixer (WAB Maschinenfabrik, Switzerland) at 90 rpm for 10 min and subsequently lubricated with 0.5% magnesium stearate. The blends were compressed into 333.33 mg tablets using a single punch press (Korsch EK0, Germany) with 10mm flat faced tooling and a compression force of 18kN.

Tablet properties and drug release measurement

Tablet weight uniformity was determined for 20 tablets. Friability and crushing strength (P) of 10 tablets each were evaluated using a friability tester (Erweka TA10) and a hardness tester (Erweka TBH30). Tablet thickness, T (mm) and diameter, D (mm) were measured using a digital micrometer. Tablet tensile strength (TS), was calculated according to Equation 1 (Fell and Newton, 1968).

$$\text{Tensile strength (\%)} = 2P/\varpi DT \qquad \text{(Equation 1)}$$

Drug release was measured in 900mL phosphate buffer pH 4.5 using the USP II paddle apparatus (Sotax, Switzerland) at 37°C and 75rpm. At pre-determined time points samples were withdrawn automatically and analyzed UV-spectrophotometrically at 272nm (Agilent 8453, USA).

3 - RESULTS & DISCUSSION

Figure 1a, b and c shows the effect of different diluents on tablet properties. Crushing strength is highest and friability lowest using MCC and DCPA followed by co-processed lactose, DCP and sucrose. Tablets containing neat maize starch could not be produced automatically due to poor flow and gave inadequate tablets with uncontrolled release (Figure 2).

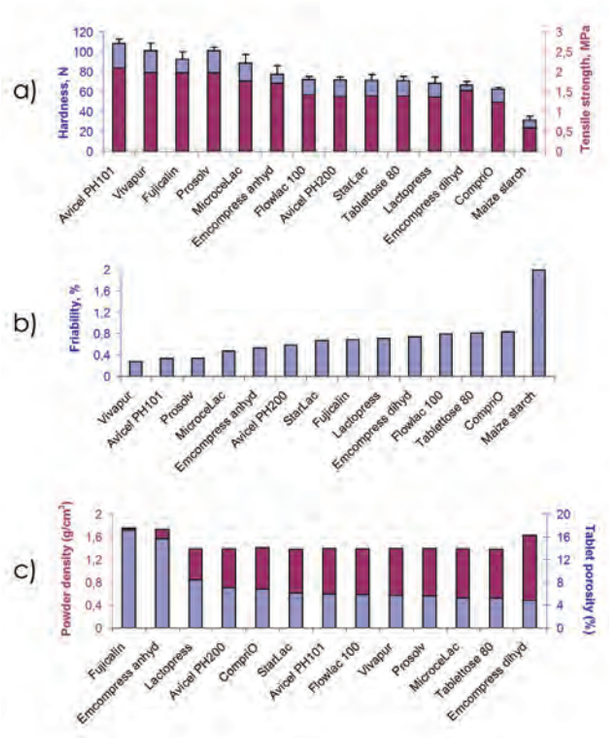

Figure 1: Effect of diluents type on tablet: a) tensile strength, b) friability and c) porosity.

Drug release profiles do not necessarily correlate with tablet hardness/friability/porosity except for maize starch. Tablets containing Avicel (MCC) released theophylline more rapidly compared to lactose and DCP(A). MCC may swell and disrupt the lipid matrix after water uptake and increase the surface area:volume ratio for drug diffusion, resulting in faster drug release. Larger MCC particles have a stronger effect on water uptake: tablets with Avicel PH200 (180µm, spherical, 2-5% moisture) broke up easier than Avicel PH101 (50µm, spherical, 3-5%) and Vivapur (90-150µm, rough, 7% moisture) (Figure 3). Compritol® tablets filled with DCP(A) gave the slowest drug release kinetic due to water insolubility of the diluent, whereas tablets with lactose (a water soluble diluent), produced faster drug release.

Interestingly, MicroceLac 100, a co-processed lactose with MCC showed better results compared to lactose and MCC alone. The reason for this might be the combination of plastic with brittle material, leading to improved tabletting properties.

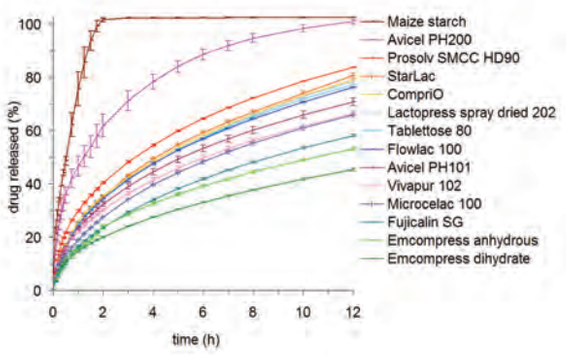

Figure 2: Drug release from Compritol® tablets containing different diluents at T zero.

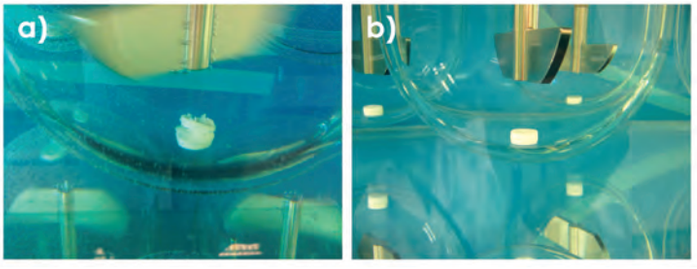

Figure 3: Aspect of tablets containing: a) Avicel PH200 and b) Avicel PH101 during drug release.

It is interesting to see that MCC particle size also impacts the drug release stability. Figures 4 and 5 show the drug release profile from tablets placed at 40°C in 75% relative humidity (RH). Whilst Avicel PH200 tablets showed a significant decrease in drug release kinetic after 3 month storage, Avicel PH101 tablets remained stable. The reason for this must be investigated in further studies.

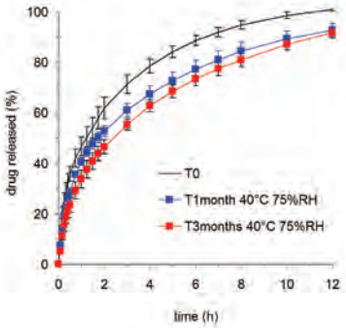

Figure 4: Drug release from tablets containing Avicel PH200 before and after 3 months storage at 40°C at 75% RH.

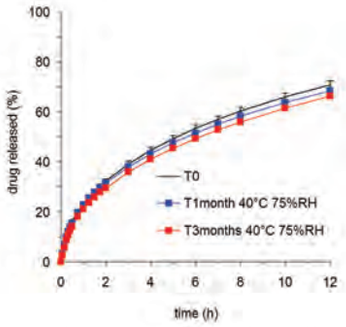

Figure 5: Drug release from tablets containing Avicel PH101 before and after 3 months storage at 40°C at 75% RH.

4 - CONCLUSION

Drug release from Compritol® matrix tablets is diffusion dominated and release rate can be readily adjusted by a number of formulation parameters. Previous studies have shown the importance of the right drug:lipid ratio to get the desired release kinetics [2]. The present study demonstrates the effect of diluent type on drug release from lipid matrix tablets: the aqueous solubility and plasticity of the diluent affects the structure of the matrix and therefore the drug release kinetics. Surprisingly, the impact of MCC on drug release and storage stability of lipid matrices was dependant on MCC grade (particle size, form and moisture level). This study shows the importance of selecting the right diluent for Compritol® 888 matrix SR tablet formulation and how diluent could be used to modulate the drug release profile.

5 - REFERENCES

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SUSTAINED RELEASE LEVODOPA MINI-TABLETS CONTAINING COMPRITOL® 888: A VIABLE APPROACH FOR SPECIAL PATIENT POPULATIONS

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1 - PURPOSE

Lipid matrix mini-tablets for the sustained-release of levodopa were manufactured using a rotary press simulator. The effects of mini-tablet size (3 & 4 mm), Compritol® 888 concentration (15 – 45 %w/w), levodopa concentration (18.75 & 37.5 %w/w) and compression speed were evaluated. Sustained-release mini-tablets with good weight uniformity, tensile strength and diffusion-controlled release rates were successfully produced over a range of compression speeds. Mini-tablets may provide compliance benefits to elderly patients and the release rate of levodopa may be modified by altering the amount of Compritol® 888 in the formulation and/or mini-tablet size, meaning that the desired release profile can be tailored to suit the clinical need.

2 - INTRODUCTION

Mini-tablets are defined as being no more than 4 mm in diameter[1] and sustained-release mini-tablets may offer clinical and compliance benefits in special patient populations[2]. Compritol® 888 is commonly used in formulating sustained-release lipid matrices and when compressed, forms an insoluble network structure, allowing water to penetrate and subsequent drug release to occur through diffusion. In a previous investigation the potential of Compritol® 888 as a non-swelling matrix-forming agent in the manufacture of theophylline sustained-release mini-tablets was demonstrated[3]. The aim of the present study was to design mini-tablets for the sustained release of levodopa (L-DOPA) for the treatment of Parkinson's disease in elderly patients and to assess the effects of mini-tablet size, Compritol® 888 (C888) concentration, drug dose and compression speed on drug release rate.

3 - EXPERIMENTAL METHODS

Investigated formulations contained: 18.75 or 37.5 %w/w levodopa, 15, 25, 35 or 45 %w/w Compritol® 888 (glyceryl dibehenate), 3 %w/w magnesium alumino silicate, 1 %w/w magnesium stearate and diluents (2:1 DCPA : Lactose). Materials were blended for 2 min and subsequently for 1 min with lubricant (2C turbula mixer). Mini-tablets of 3 and 4 mm diameter (20 and 40 mg target weights respectively) were produced using a Stylcam® 100R rotary-press simulator with flat-faced tooling at compression forces of 2-4 kN and speeds of 10-30 rpm. Mini-tablet strength (kp) was determined using a Pharmatron 6D tester and tensile strength calculated based on tablet thickness (mm) and diameter (mm). Drug release was evaluated using a Varian VK7000 dissolution tester and a Cary 50 UV spectrophotometer at 280 nm. Data were analysed using the equation $Q = K\,t^n$, where Q is the fraction of drug release at time t, K is a kinetic constant and n is the exponent indicative of the release mechanism.

4 - RESULTS AND DISCUSSION

All formulations displayed good flowability, enabling the production of mini-tablets with excellent weight uniformity (CV <2%) under simulated rotary-press production conditions (Table 1). Robust mini-tablets were successfully produced from all formulations. Tensile strength was inversely proportional to the percentage of Compritol® 888 in the formulation but was independent of compression speed (Table 2).

The rate of drug release decreased as the concentration of Compritol® 888 and the mini-tablet diameter increased due to the tortuosity of the matrix and the length of the diffusion pathway respectively. Drug release rate was independent of compression speed. The total amount of drug released from mini-tablets comprising 18.75 %w/w Levodopa varied between 50% from 4 mm mini-tablets with 45 %w/w Compritol® 888 (Figure 1) to 100% from 3 mm mini-tablets with 15%w/w Compritol® 888 (Figure 2). Drug release from mini-tablets comprising a higher dose (37.5%w/w Levodopa) was faster, but sustained-release profiles were achieved even at relatively low levels of Compritol® 888 (Figure 3 & Figure 4). Analysis of data revealed drug release rates were proportional to the square-root of time (n ≈ 0.5), indicating a diffusion-controlled release mechanism.

Table 1: Weight uniformity (mg) of mini-tablets (mean ± SD, n = 10).

Production Speed	3 mm mini-tablets					4 mm mini-tablets				
	18.75% L-DOPA				37.5% L-DOPA	18.75% L-DOPA				37.5% L-DOPA
	15% C888	25% C888	35% C888	45% C888	25% C888	15% C888	25% C888	35% C888	45% C888	25% C888
10 RPM	20.0 ±0.2	20.8 ±0.2	19.8 ±0.2	20.0 ±0.4	20.0 ±0.2	39.7 ±0.4	39.9 ±0.4	40.9 ±0.4	40.5 ±0.5	39.8 ±0.5
20 RPM	20.1 ±0.2	20.2 ±0.2	19.6 ±0.3	20.0 ±0.3	19.9 ±0.2	39.9 ±0.2	39.3 ±0.3	40.2 ±0.6	40.8 ±0.3	39.5 ±0.6
30 RPM	20.1 ±0.1	20.2 ±0.2	19.5 ±0.2	19.8 ±0.2	19.8 ±0.3	40.3 ±0.4	39.1 ±0.1	39.1 ±0.3	41.1 ±0.1	39.3 ±0.2

Table 2: Tensile Strength (MPa) of mini-tablets (mean ± SD, n = 10).

Production Speed	3 mm mini-tablets					4 mm mini-tablets				
	18.75% L-DOPA				37.5% L-DOPA	18.75% L-DOPA				37.5% L-DOPA
	15% C888	25% C888	35% C888	45% C888	25% C888	15% C888	25% C888	35% C888	45% C888	25% C888
10 RPM	1.8 ±0.4	1.4 ±0.3	1.4 ±0.2	1.1 ±0.2	1.4 ±0.3	1.7 ±0.1	1.4 ±0.3	1.5 ±0.2	1.0 ±0.2	1.2 ±0.2
20 RPM	1.6 ±0.2	1.3 ±0.2	1.3 ±0.1	1.2 ±0.3	1.2 ±0.2	1.9 ±0.3	1.4 ±0.2	1.4 ±0.2	1.0 ±0.2	1.2 ±0.3
30 RPM	1.5 ±0.1	1.4 ±0.1	1.4 ±0.3	1.1 ±0.3	1.1 ±0.2	1.8 ±0.2	1.3 ±0.2	1.3 ±0.1	0.9 ±0.1	1.1 ±0.1

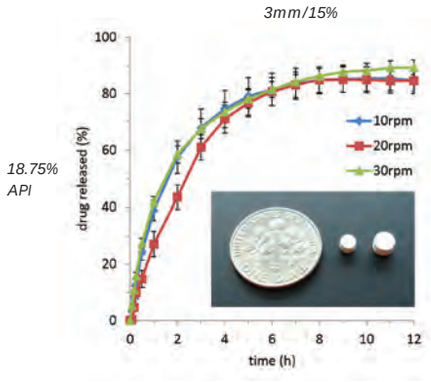

Figure 1: Drug release from 3mm mini-tablets containing 18.75%w/w (3.75mg) L-DOPA & 15%w/w Compritol® 888 produced at different speeds (mean ±SD, n=6).

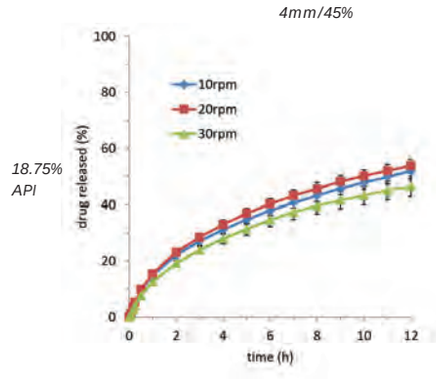

Figure 2: Drug release from 4mm mini-tablets containing 18.75%w/w (7.5mg) L-DOPA & 45%w/w Compritol® 888 produced at different speeds (mean ±SD, n=6).

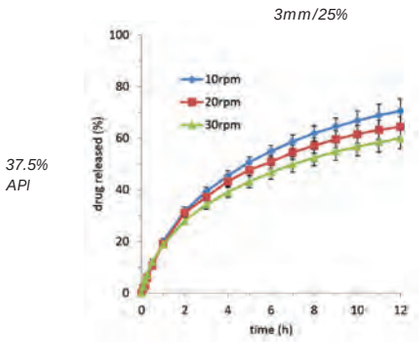

Figure 3: Drug release from 3 mm mini-tablets containing 37.5%w/w (7.5mg) L-DOPA & 25%w/w Compritol® 888 produced at different speeds (mean ±SD, n=6).

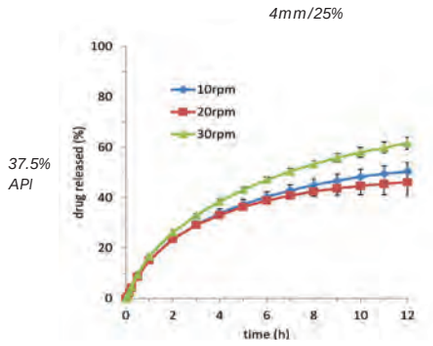

Figure 4: Drug release from 4mm mini-tablets containing 37.5%w/w (15mg) L-DOPA & 25%w/w Compritol® 888 produced at different speeds (mean ±SD, n=6).

5 – CONCLUSION

Sustained-release levodopa mini-tablets (3 & 4mm) were successfully manufactured under simulated rotary press production conditions. The release rate of levodopa from sustained-release mini-tablets may be modified by altering the amount of Compritol® 888 in the formulation and/or mini-tablet size, meaning that the desired release profile can be tailored to suit the clinical need. The small size of mini-tablets may provide compliance benefits in special patient populations.

6 – REFERENCES

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[2] Mohamed, F (2013) The influence of formulation parameters in the development of extended-release mini-tablets. PhD Thesis, Liverpool John Moores University, UK.
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HIGH DRUG LOAD LIPID MATRIX TABLETS PREPARED BY WET GRANULATION: PART I - FORMULATION PARAMETERS

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1 - PURPOSE

Nicotinic acid (niacin) is a micronized API with poor flow properties making the production of high dose sustained release tablets by direct compression a real challenge. This study aims to evaluate wet granulation as a simple and efficient process to obtain high dose niacin sustained release lipid matrix tablets.

2 - INTRODUCTION

Micronized drugs have poor flow properties which make the production of high dose tablets by direct compression difficult due to homogeneity, dust generation and process variability. The drug developers usual recourse is to formulate such compounds by a wet granulation process.

Compritol® 888 ATO (glyceryl dibehenate NF) is frequently used in sustained release systems. It is a triacylglyceride (glycerol esterified with behenic acid), with a HLB of 1 and a melting point of 70°C. Insoluble and lipophilic, it forms a release retarding matrix which entraps drug and slowly releases it by diffusion over several hours. Being insoluble in aqueous fluids, Compritol® 888 is well-suited for wet granulation in contrast to hydrophilic polymers that may swell causing the formation of lumps [1]. The study describes the development of sustained-release niacin tablets with Compritol® 888 using a wet granulation process.

3 - EXPERIMENTAL METHODS

Niacin properties have been determined using a binocular loop and a flow tester. Niacin was blended with Compritol® 888 ATO at varying ratios. A mortar and pestle were used to granulate the powders with the addition of water. The impact of a binder (Kollidon® 30, PVP, BASF) in the powder blend was evaluated. Granules were sieved, dried overnight at 40°C in a dry oven and compressed into flat faced tablets (Korsch EK0, 14kN, 16mm/12mm), using 0.5% magnesium stearate as lubricant. The drug dose was 500 or 1000mg. Drug release studies were conducted in a USP II paddle apparatus (900mL 0.1N HCl, 37°C, 100rpm) and the dissolution profiles compared by application of the similarity factor f2.

4 - RESULTS AND DISCUSSION

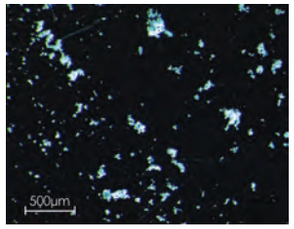

Figure 1: Macroscopic image of micronized niacin.

Table 1: Flow behavior of micronized niacin.

Niacin properties	100g
Flowability, s	n.d.
Angle of repose, °	>60
Haussner ratio	1.76
Carr's Index, %	43

n.d. = not detectable

Table 2: Composition of tablets prepared by wet granulation.

Ingredients		%w/w
Nicotinic acid	Granules	0-91.7
Compritol® 888 ATO		q.s.
Kollidon® 30 (if indicated)		3
Mg Stearate		0.5

Micronized niacin has a particle size of 34µm (Figure 1) and exhibits very poor powder flow and compressibility (Table 1). Powder-flow is improved by granulating niacin with Compritol® 888 ATO using water as binder. The resulting granules showed good flow properties and were easily compressed into tablets. Drug release was sustained over at least 12h depending on the niacin:Compritol® ratio (Figure 2). Importantly, drug release from 90:10 blends was slowed down by simply changing the tablet dimension due to the longer drug diffusion pathway (Figure 3). However, granule cohesion was limited and tablets therefore tended to stick to the punch.

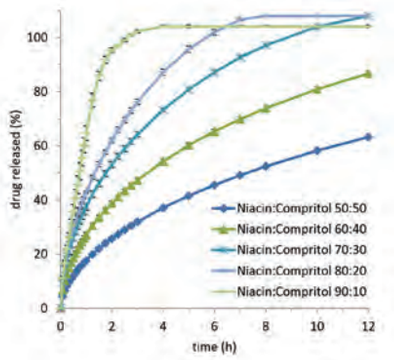

Figure 2: Drug release from tablets containing granules with various niacin/Compritol® ratios (dose 500mg, no binder).

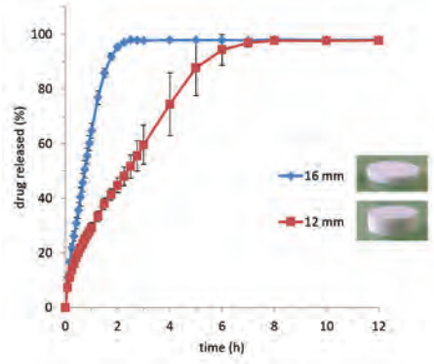

Figure 3: Impact of tablet dimension on drug release (dose 500 mg, drug:lipid ratio 90:10).

The addition of 3% of PVP yielded tablets with an approximately two-fold increase in tensile strength (Figure 4). Adhesion to the punch was prevented, resulting in tablets with a smooth surface. The increase in tablet tensile strength slightly reduced drug release over time but not significantly (Figure 5). The niacin:Compritol® 888 ratio affected tablet size with higher drug loads producing smaller tablets (Figure 6). This is of particular interest since higher drug loads generally produce large cumbersome tablets.

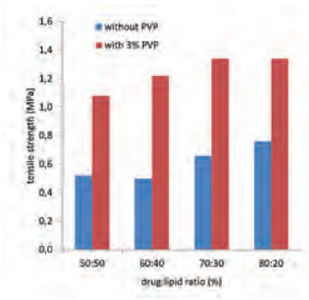

Figure 4: Effect of binder addition on tablet tensile strength.

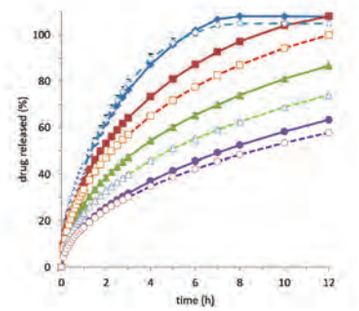

Figure 5: Influence of PVP on niacin release: filled symbols without PVP, open symbols with PVP (dose 500mg).

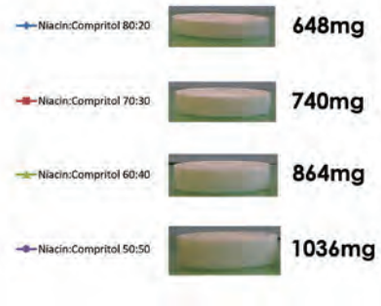

Figure 6: Effect of the drug:lipid ratio on tablet height and weight (dose 500mg).

1000mg niacin tablets were prepared varying the drug:lipid ratios and the results indicate that drug release can be effectively sustained using 10% of Compritol® 888 (Figure 7). Drug release kinetics similar to the marketed product Niaspan® were obtained (f2>50). The low Compritol® 888 concentration enables a reasonable tablet weight to be maintained despite high drug loading (Figure 8). Again, tablet height was affected by the drug:lipid ratio (Figure 8).

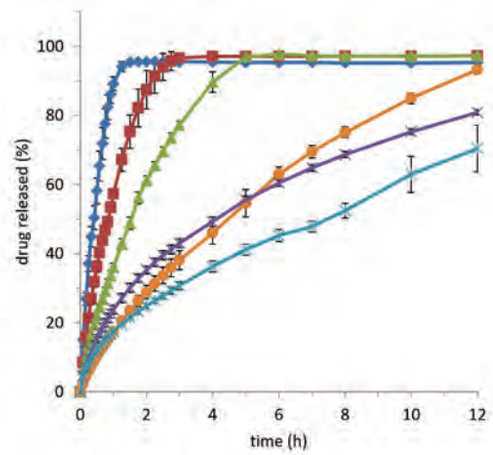

Figure 7: Drug release from tablets containing different niacin/Compritol® ratios (dose 1000mg).

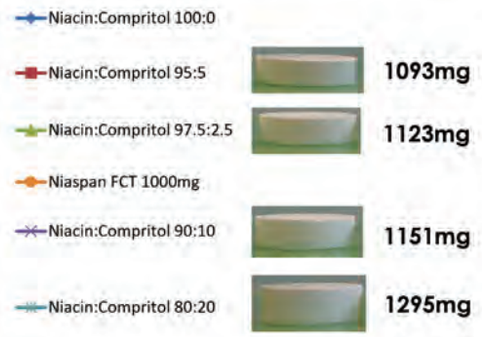

Figure 8: Effect of the drug:lipid ratio on tablet size and weight (dose 1000mg).

5 - CONCLUSION

Being a micronized and freely soluble drug, sustained release niacin tablets can be challenging to formulate. The formulation of a lipid matrix tablet by simple wet granulation-compression is a viable approach. The addition of PVP is shown to improve the quality of tablets with limited effect on drug release. High dose lipid matrix tablets delivered sustained release comparable to an existing authorized medicine. The ratio of drug to excipient enables tablet height and size to be considered as part of the overall dosage form design.

6 – REFERENCES

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HIGH DRUG LOAD LIPID MATRIX TABLETS PREPARED BY WET GRANULATION: PART II – PROCESS PARAMETERS

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1 - PURPOSE

The rationale for a wet granulation process for the production of high dose niacin lipid matrix sustained release tablets was demonstrated in part I of this study. In part II the effects of process parameters on granule growth of niacin: Compritol® 888 blends, subsequent tablet properties and drug release rates are evaluated.

2 - INTRODUCTION

Part I of the study describes a wet granulation process with niacin in a Compritol® 888 ATO matrix using a mortar and pestle. In part II the process parameters are evaluated in a fluid bed granulator (FBG) with focus on granule growth, physical properties and drug release. The identification of critical parameters is crucial to implement PAT (Process Analytical Technology) according to the principles of Quality by design [1].

3 - EXPERIMENTAL METHODS

600g of Compritol® 888 ATO and niacin ratio 1:1 were blended with 3% (w/w) PVP for 5 min at 90 rpm, fluidized for 5 min and granulated in a Glatt GPCG1.1 at varying processing conditions (Table 1). Granules were dried until the product reached the outcome temperature, and moisture content measured. PVP was added in different concentrations or as 3% binder solution. Particle size distribution and granule properties were analyzed prior to tabletting (Korsch EK0) with 0.5% magnesium stearate as lubricant. Dissolution studies were conducted in 0.1N HCl (USP II, 900 mL, 100 rpm, 37°C). Drug dose was 500mg.

Table 1: Investigated process parameters (niacin:Compritol® 1:1)

	3% PVP						10% PVP	20% PVP
Parameter	**FBG 1**	**FBG 2**	**FBG 3 (A/B)**	**FBG 4**	**FBG 5**	**FBG 6**	**FBG 7**	**FBG 8**
Inlet temperature, °C	40	40	40	65	65	65	40	40
Product temperature, °C	25	24	24	41	35	36	30	32
Drying temperature, 0C	45	45	45	65	65	65	65	65
Spray rate, g/min	8	16	24	24	24	24	24	24
Atomization pressure, bar	1	1	1	1	1	2	2	2
Granulation liquid (water), %	17	17	17	34	17	34	34	34

4 - RESULTS AND DISCUSSION

Table 1 describes all the granulation conditions (FBG1 to 8). All 8 processing conditions resulted in particle growth compared with physical mixture (Figure 1). Increasing atomization pressure in combination with higher water concentration (FBG3 vs. FBG6) and higher PVP concentration (FBG6 vs. FBG7 vs. FBG8) affected granule size. The critical parameters for the niacin:Compritol® formulation and the effect on granule and tablet properties are listed in Table 2.

Table 2: Critical parameters and effects on granule/tablet properties.

Critical parameters	**FBG 3A**	**FBG 3B**	**FBG 6**	**FBG 7**	**FBG 8**
Atomization pressure, bar	1	1	**2**	2	2
PVP CONCENTRATION, %	3	3 (solution)	**3**	10	20
Granule properties					
Mean particle size, µm	99.2 (±53.4)	112.7 (±57.3)	**134.5 (±69.5)**	313.6 (±160.3)	448.3 (±230.9)
Carr's Index, %	20	15	**16**	12	12
Bulk density, g/cm³	0.4	0.46	**0.43**	0.46	0.46
Haussner ratio	1.26	1.17	**1.18**	1.14	1.14
Tablet characteristics					
Weight variation, %	0.35	0.16	**0.3**	0.22	0.19
Tensile strength, MPa	1.0	0.95	**1.1**	0.94	0.72
Friability, %	0.57	0.58	**0.66**	0.74	0.77

Granule growth increased with increasing PVP concentration due to improved powder wetting (Figure 2). The optimum flowability was obtained with 10% of PVP and remained unchanged with 20% of PVP, despite further granule growth. Tablets made with larger granules had the lowest weight variation, but also the lowest tablet hardness (due to increased bulk density and reduced surface area available for inter-particulate bonding). The addition of PVP in the binder solution resulted in larger granules with better homogeneous size distribution compared to the addition of dry PVP to the powder blend. This is again likely to improved wetting (Figure 2). Tablets made with larger granules (FBG7 & FBG8) showed slower release rates compared to tablets made with smaller particles (FBG3A, FBG 3B, Figure 3). The process parameters (FBG 3 vs FBG 6) had no significant influence using 3% of dry PVP (Figure 4).

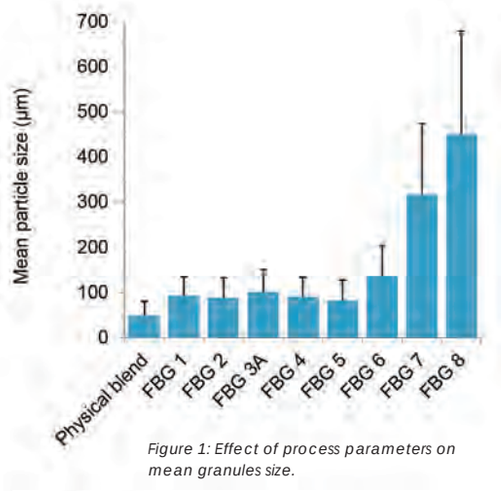

Figure 1: Effect of process parameters on mean granules size.

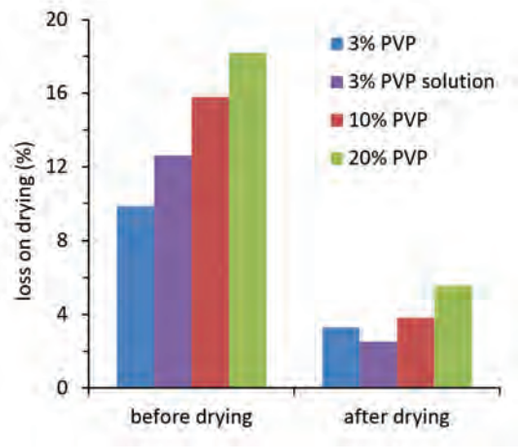

Figure 2: Effect of PVP concentration on LOD of granules.

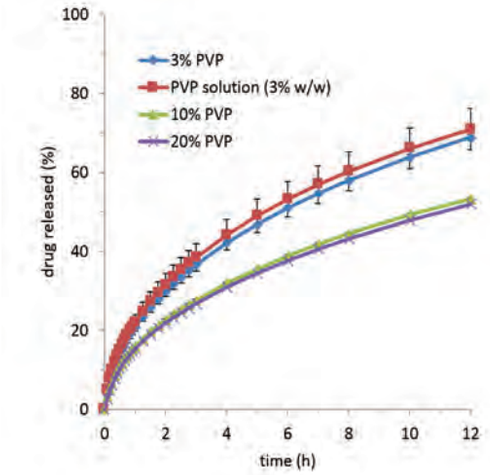

Figure 3: Effect of PVP concentration on drug release.

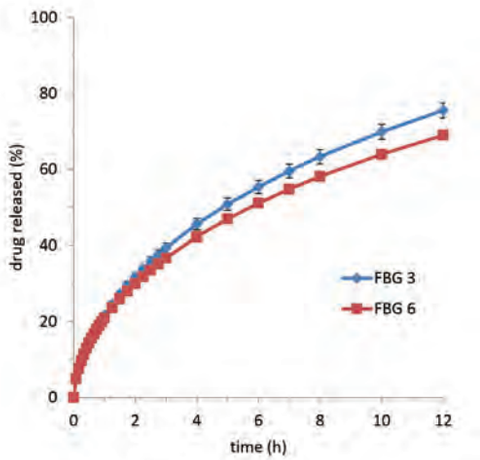

Figure 4: Effect of process parameters on drug release.

5 - CONCLUSION

Granule growth was affected by higher atomization pressures and PVP amounts. Tablet properties and drug release were markedly affected by binder concentration and only slightly by process conditions. Process conditions in FBG3B, FBG6 and 7 produced optimum granules (good flow and compressibility). These findings can be useful during formulation development and construction of the design space following the principles of QbD.

6 – REFERENCES

[1] Yu, L.X. April 2008, Volume 25, Issue 4, pp 781-791.

PERCOLATION THRESHOLD OF COMPRITOL® 888 IN MATRIX TABLET : ASSESSING THE MINIMUM CONCENTRATION TO CREATE AN INFINITE LIPID NETWORK

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1 - PURPOSE

The efficacy of Compritol® 888 as sustained release matrix former has been widely demonstrated with various techniques. This study was designed to evaluate the minimum excipient concentration necessary to create an infinite matrix network to obtain sustained and reproducible drug release.

2 - INTRODUCTION

Reproducible sustained release (SR) matrix systems rely on the use of a minimum concentration of excipient to create an infinite matrix network which entraps drug and prevents its immediate release [1]. This minimum excipient concentration is referred to as the 'percolation threshold' and should be considered when designing a SR matrix system. The percolation threshold concept is well-described for hydrophilic polymer matrices, with 20 – 30% excipient content being cited [2,3]. Our study concerns Compritol® 888 ATO (glyceryl dibehenate NF), a lipid matrix former frequently used to sustain drug release. Insoluble and lipophilic, with a hydrophilic-lipophilic balance (HLB) of 1 and a melting point of 70°C, it forms a release retarding matrix for freely water soluble drugs and controls release by diffusion.

3 - EXPERIMENTAL METHODS

20% theophylline (100mg), 5 – 40% w/w of Compritol® 888 ATO and diluents (DCPA:Lactose ratio 1:1) were blended for 10min at 90rpm and lubricated with 0.5% magnesium stearate prior compression into 12mm flat faced tablets using a single punch press. Tablets were analyzed for tensile strength, mass uniformity, friability and drug release using a USP II apparatus (900mL phosphate buffer pH 4.5 if not otherwise stated, 37°C, 75rpm). The percolation threshold of Compritol® 888 was evaluated: (i) by plotting the Peppas slopes (Equation 1) versus the lipid percentage [4], (ii) by determining the change in the apparent drug diffusion coefficient in these lipid matrices (Equation 2) and (iii) by tablet aspect after dissolution.

Equation 1 $$\frac{M_t}{M_\infty} = k \cdot t^n$$

Equation 2 $$\frac{M_t}{M_\infty} = 4 \cdot \sqrt{\frac{D \cdot t}{\pi \cdot R^2}} - \frac{D \cdot t}{R^2}$$

Where M(t)/M(∞) denotes the cumulative amounts of drug released at time t and infinity respectively, k is the release constant, n is the diffusional exponent, D the diffusion coefficient, R the tablet radius and t the time.

4 - RESULTS AND DISCUSSION

All Compritol® 888 concentrations >5% provided prolonged theophylline release over at least 12h (Figure 1a). Release rates decreased with increasing Compritol® 888 and decreasing diluents concentration due to enhanced lipophilicity of the matrix and less pore formation. From 40% Compritol® 888 matrices 100% of the drug were recovered only after 72h.

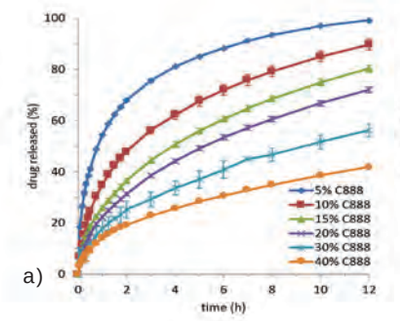

Figure 1a: Theophylline release from lipid matrix tablets with varying Compritol® concentrations.

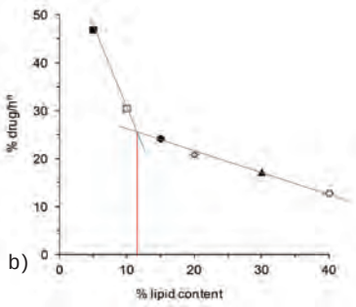

Figure 1b: Pappas' slopes vs Compritol® 888 percentages.

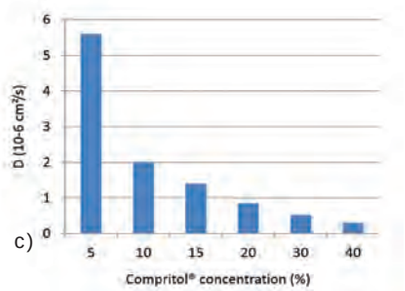

Figure 1c: Apparent diffusion coefficient of theophylline from these lipid matrices.

The Peppas power law was applied to describe the underlying mass transport mechanism. All n values were below 0.47, indicating diffusion dominated drug release. The Peppas slopes are correlated with the percentages of Compritol® 888, where the intersection of the linear regressions represents the critical concentration of lipid of >10% (Figure 1b). Calculation of the diffusion coefficient also indicates that >10% is a critical amount in this formulation. At 5% Compritol® 888 concentration drug motility is high correlating with fast, "uncontrolled" diffusion of water soluble compounds – including the drug - out of the system, indicating an non-infinite matrix system is present. At >10% Compritol® 888 drug release is much slower and controlled, a consequence of reduced drug mobility and indicative of a more finite lipid network in the system.

Evaluation of tablet aspect confirms this: the 5% Compritol® 888 tablets were almost completely eroded after 12 hours of dissolution whilst erosion was less apparent for matrices containing 10% lipid excipient (Figure 2).

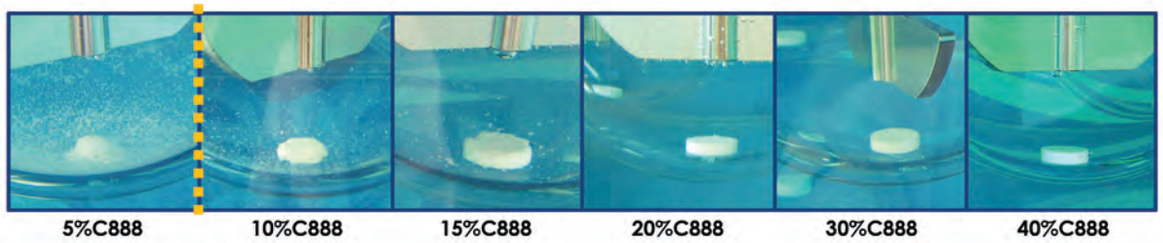

Figure 2: Tablet aspect after 12h of dissolution for different Compritol® 888 concentrations.

These results combined with the analysis of Peppas slope and drug diffusion coefficient indicate that the percolation threshold for Compritol® 888 in this formulation is ≥ 10%. Hence, tablets containing 15% of Compritol® 888 were further investigated for robustness ie. effects of pH, ethanol and paddle speed on drug release. Figure 3 and 4 summarize the results: no significant changes in drug release were observed in the presence of various pH and 40% ethanol or increasing paddle speed, indicating good robustness.

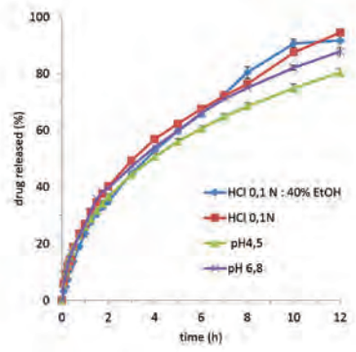

Figure 3: Effect of pH changes and the presence of ethanol on drug release.

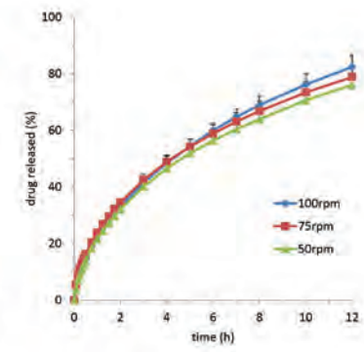

Figure 4: Effect of dissolution paddle speed on drug release.

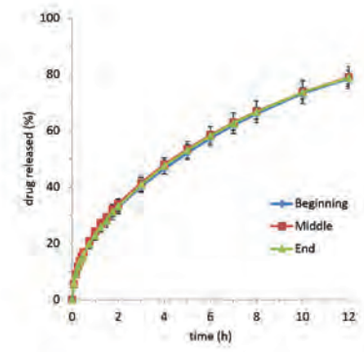

Figure 5: Theophylline release from tablets taken at different production time points.

Scaling-up of the formulation and transfer to a multi punch press (10 punch RIVA Piccola) was successful. Tablets taken at different production time points exhibited similar properties and very low drug release variations (1.5±0.8%, Figure 5) with good reproducibility (f2 values of 97, 95 and 90 respectively for 3 different batches released under identical conditions).

5 - CONCLUSION

In this formulation the minimum Compritol® 888 concentration (ie. percolation threshold) is ≥ 15% by weight. This concentration provides reproducible sustained drug release from robust matrices produced by direct compression. In addition, the tablet properties and drug release profile were reproducible when scaled-up to multi-punch press, suggesting a robust formulation design approach.

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SYNERGIC EFFECT OF TWO GLYCERIDES TO INCREASE STABILITY AND ETHANOL RESISTANCE OF SUSTAINED RELEASE MATRIX TABLETS

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1 - PURPOSE

Lipid matrix tablets provide an attractive and practical approach to sustain the release of highly water soluble drugs. Lipid matrices are non-swellable and are insensitive to environmental and physiological conditions such as humidity or pH changes. Therefore, a tablet film coating is not required. However, the strength or robustness of a lipid matrix is dependent on both formulation and processing parameters. Sintering is a post-compression heat treatment frequently described in the literature as an excellent procedure to reinforce lipid matrix tablets, however the technique is not used industrially due to the processing conditions (80°C). This study demonstrates how to obtain the same benefits as sintering using standard curing conditions; the formulation utilizes Compritol® 888 ATO as the matrix former by direct compression and Precirol® ATO 5 as the matrix reinforcer by curing.

2 - INTRODUCTION

Compritol® 888 ATO is a lipid excipient frequently used in sustained release applications. It is composed of glycerol behenate exhibiting a HLB of 1 and a melting point of 70°C. Due to its lipophilic nature and reduced wettability, drug delivery can be successfully extended over prolonged periods of time and might be highly effective even for freely water soluble drugs.

Compritol® is not soluble in alcohol and therefore the lipid matrix structure produced by direct compression is not dissolvable in alcohol. This means the matrix is not subject to hydro-alcoholic media. However if the API has a higher solubility in hydro-alcoholic media, direct compression produces a lipid matrix with limited robustness because the mechanism of diffusion will be faster due to higher driving force.

However, it has been shown that a post-heat treatment on tablets or a hot process can generate a lipid belt that enhances the alcohol resistance. Sintering technique has been studied with Compritol® 888 when tablet obtained by direct compression was placed in a dry oven to 80°C. This extreme condition is not well accepted by industrials and then alternative lipids with lower melting point might be more adapted.
Interestingly, Precirol® ATO 5 has a lower melting point 54°C and can be associated with Compritol® 888 ATO in tablet. A simple curing step at 60°C can melt Precirol® ATO 5 within the tablet.

3 - EXPERIMENTAL METHODS

Theophylline anhydrous was selected for this study because it is a water soluble drug (Table 1) and it is available in sustained release dosage forms. It is an interesting model for alcohol dose dumping since its solubility is enhanced by a factor of three in 0.1 N HCl with 40% ethanol (Table 2).

Table 1: Theophylline description.

Therapeutic Class	Bronchodilator
Water solubility at 25°C	1-5 mg/mL
Half-life	8 hours
Dose	100 – 600 mg
Melting point	272°C
pKa	8.81, weak base

Table 2: Theophylline solubility in various release media at 37°C.

Solubility, mg/mL	
0.1 N HCl	11.46
0.1 N HCl + 40% Ethanol	31.68
phosphate buffer pH 6.8	10.41
phosphate buffer pH 4.5	9.60

Compritol® (glyceryl behenate - USP/NF) is used in the formulation as matrix former and Precirol® (glyceryl distearate - USP/NF) as a matrix reinforcer. A blend of diluents were added in order to get a conform hardness and weight in the final tablet (Table 3).

Table 3: Tablet formulation.

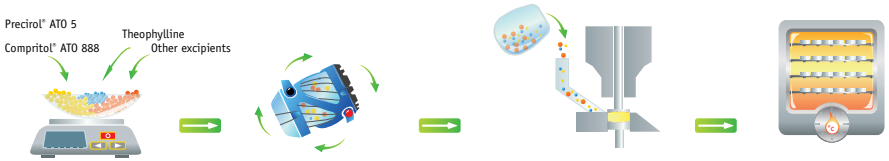
Ingredients	Supplier	mg/tablet	% w/w
Theophylline anhydrous	Sigma-Aldrich	100	16.7
Compritol® 888 ATO (glyceryl behenate)	Gattefossé	90	15.0
Precirol® ATO 5 (glyceryl distearate)	Gattefossé	60	10.0
Fujicalin SG (dibasic calcium phosphate anhydrous)	Fuji Chemical	217	36.2
Flowlac 100 (spray-dried lactose)	Meggle Pharma	109	18.1
Neusilin US2 (Mg-Al-metasilicate)	Fuji Chemical	18	3.0
Mg-stearate	Sigma-Aldrich	6	1.0
Total tablet weight		**600 mg**	**100%**

Lipid matrix tablets were prepared by direct compression using theophylline anhydrous, diluents and a blend of Compritol® 888 ATO and Precirol® ATO 5. All tablets were prepared on an alternative tabletting machine (Korsch Ek03). The contact angle on the tablet surface was measured using a goniometer ILMS from GBX instruments. A 3 µl droplet of demineralized water was used and pictures were taken during 90 s.

Tablets were then exposed to a curing at 60°C for 30 min in a dry oven. Dissolution studies were conducted in 0.1 N HCl (with or without 40% ethanol) and in phosphate buffer pH 4.5 using the USP II paddle apparatus.

Drug absorption was measured by UV. Stability studies were conducted on tablets placed in accelerated storage conditions at 40°C/75% RH in closed containers.

Figure 1: Direct compression followed by curing at 60°C during 30 min.



4 - RESULTS AND DISCUSSION

Glycerides are non-ionic: hence the lipid matrix is not impacted by pH changes. However diffusion rate from the matrix can be influenced by drug solubility. For Theophylline, there is no difference of drug release when tablet is exposed to various pHs (Figure 2).

Glycerides are non soluble in ethanol and therefore the lipid matrix is not subject to alcohol dose dumping. For Theophylline, being more soluble in ethanol than in water, it is likely that the diffusion rate will be faster from a tablet. Then it is important to apply a hot melt treatment to fuse the drug with lipids that reduces its surface of contact with ethanolic media. The simple curing at 60°C for 30 minutes generates the melt of Precirol® ATO 5 in the tablet and confers a cement-like network that makes Theophylline diffusion independent from alcohol content (Figure 3).

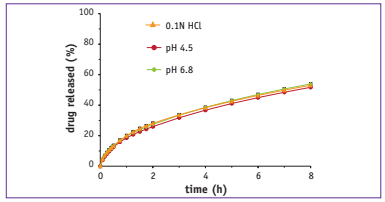


Figure 2: Effect of pH on theophylline release from Compritol® 888: Precirol® ATO 5 matrix tablets.

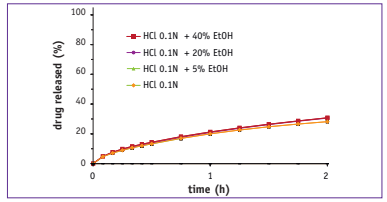


Figure 3: Influence of ethanol concentrations on theophylline release from Compritol® 888 ATO:Precirol® ATO 5 matrix tablets.

Interestingly, pictures showing the angle of contact of water on the tablet surface demonstrate that the curing treatment at 60°C increases the lipophilicity of the tablet surface.

The angle of contact was increased from 86° before curing to 125° after curing. Figure 4 shows how the droplet of water wets the tablet surface during 90 seconds. For a non-cured tablet, water droplet collapses slowly because it starts to dissolve hydrophilic ingredients on the surface.

For the cured tablet, Precirol® has created a lipid film on the surface so that the water droplet remains spherical during the 90 seconds. The presence of this film confirms that Precirol® ATO 5 melts during the curing step and confers a cement-like network within the tablet, which renders the surface lipidic.

Angle of contact = 86° (for tablet before curing)

Angle of contact = 125° (for tablet after curing)

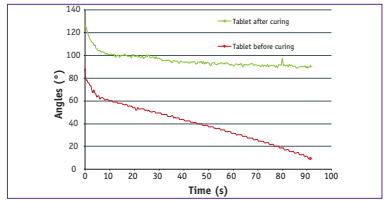


Figure 4: Variation of the contact angle function of time (s.).

To study the long term stability of the lipid matrix, tablets were placed into an oven at 25°C/60% RH and 40°C/75% RH. Figures 5 and 6 show that drug release is stable for 5 months. The study is still ongoing.

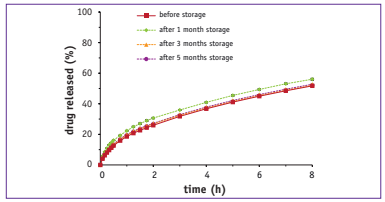


Figure 5: Dissolution of tablets in phosphate buffer pH 4.5. Stability of Compritol® 888:Precirol® ATO 5 matrix tablets upon long term storage at 25°C/60% RH.

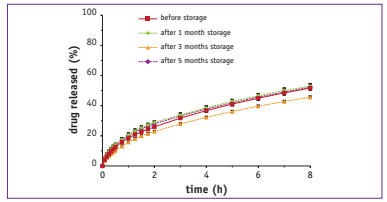


Figure 6: Dissolution of tablets in phosphate buffer pH 4.5.Stability of Compritol® 888:Precirol® ATO 5 matrix tablets upon long term storage at 40°C/75% RH.

5 - CONCLUSION

The combination of Precirol® ATO 5 and Compritol® 888 ATO in lipid matrix tablets can offer a great opportunity to increase the tablet stability and robustness for drug subject to alcohol dose dumping.
The process is straightforward: direct compression followed by a short curing step at 60°C for 30 min.

COMPRITOL® 888 ATO LIPID MATRICES FOR SUSTAINED RELEASE PROCESSED BY HOT-MELT EXTRUSION

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ABSTRACT SUMMARY

In the current study we explored the efficiency of Compritol® 888 ATO, a lipid excipient, for the manufacture of sodium diclofenac (DfNa) sustained release matrices by using Hot Melt Extrusion (HME) processing. The extrudates were processed with a twin screw Eurolab 16 extruder and the pellets obtained were further milled to produce granules.

Different HME processing approaches were used including "cold" extrusion where drug/lipid binary blends at different ratios were processed at temperatures below the lipid's melting point. The blends were also extruded at temperatures above the lipids' melting point and the extruded granules were used in tablet formulations made by direct compression at different compaction forces. In addition pre-blended tablet formulations were extruded to investigate the effect on drug release. Furthermore, the extrudates were characterized by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and hot stage microscopy (HSM) in order to identify the state of the active substance within the lipid matrix.

INTRODUCTION

HME extrusion has been used for the development of various solid dosage forms aiming to increase the solubility of poorly soluble drugs, taste mask bitter substances and control drug release mainly by using thermoplastic polymers after the addition of plasticizers.

There are only a few studies refering to lipid extrusion for taste masking and sustained release where, during the HME processing the materials were extruded mainly at temperatures below the melting point of the lipid[1,2].

Glyceryl behenate (Compritol® 888 ATO) is a hydrophobic fatty acid ester of glycerol with a HLB of 1 and a melting point 70°C. It is a fine white powder with a mean particle diameter of 50 µm used in tablet processing as a lubricant or as a lipid matrix former for sustained release. The mechanism of drug release is primarily diffusion through the insoluble, non-swellable matrix. In the current study, the effect of the drug/lipid ratio and the processing parameters on the dissolution rate of DfNa was investigated.

EXPERIMENTAL METHODS

The DfNa/Compritol® 888 ATO blends (at ratios of 30:70, 40:60 and 50:50, Table 1) were mixed in 100 g batches for 10 min in a Turbula TF2 mixer. The extrusion was performed using a Eurolab 16 twin screw extruder using various temperatures and 50 rpm screw speed. The extrudates were milled by ball milling with a rotational speed of 200 rpm for 2 mins each.

The extruded granules were then blended with standard tablet excipients and compressed under different compaction forces using a Flexitab tablet press to produce tablets with 10, 15 and 20kP hardness strength. The granules were characterized by XRPD, DSC, HSM and dissolution studies were carried out in 900 ml distilled water at 37°C, 100 rpm.

RESULTS AND DISCUSSION

Due to the properties of Compritol® solid extrudates (Batches A, B and C) of DfNa were initially prepared by "cold" extrusion processing at temperatures below the melting point of Compritol® (<58°C).
The same batches were processed at extrusion temperatures above the melting point of Compritol® (73°C).
The pre-mixed formulations were extruded at higher temperatures because of the presence of other excipients (e.g. fujicalin, neusilin) with maximum processing temperatures of 85°C.

Fig. 1 shows the X-ray patterns of the extruded granules; the DfNa intensity peaks indicate the presence of crystalline drug within the polymer matrix.
Similar intensity peaks were observed for higher DfNa ratios even after the processing of the pre-mixed batches. As a result DfNa is not solubilised in the lipid matrix during the HME processing.

Table 1: Composition of tablet formulations process by HME.

Materials	Batch A 30:70 (%)	Batch B 40:60 (%)	Batch C 50:50 (%)
DfNa/Compritol® 888 ATO extr.	55	55	55
Dibasic calcium phosphate anhydrous (Fujicalin)	14.0	14.0	14.0
Lactose (Lactopress)	27.0	27.0	27.0
Magnesium alumino metasilicate (Neusilin)	3.0	3.0	3.0
Magnesium stearate	1.0	1.0	1.0

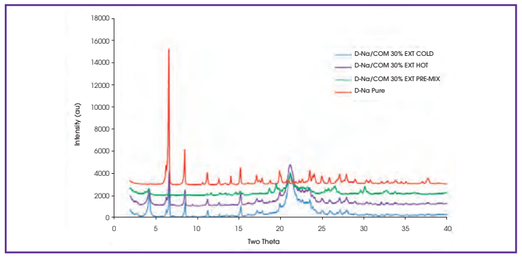

Fig. 1: X-ray diffraction patterns of pure DfNa and extruded DfNa/Compritol® 888 ATO (30:70) granules.

The XRPD results were confirmed by DSC scans of the extruded batches. In Fig. 2b, DfNa melting endothermic peaks were shifted to lower temperatures (238-243°C) compared to the pure substance. Even at high DfNa loading ratios (50/50) a clear endothermic peak can be observed.

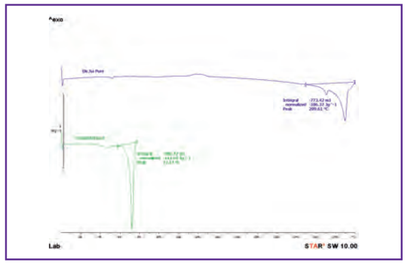

Fig. 2a: DSC scans of pure DfNa, Compritol® 888 ATO.

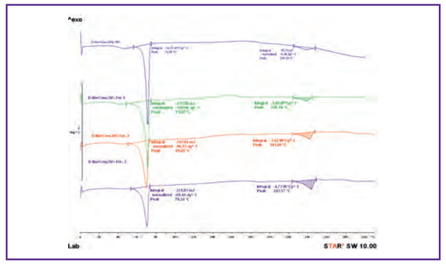

Fig. 2b: DSC scans of hot extruded DfNa/Compritol® 888 ATO granules at different ratios.

Fig. 3 shows the effect of the HME processing on the DfNa dissolution profiles. Drug dissolution varied depending on the extrusion process, the drug/lipid ratio and the tablet hardness.

The "cold" extruded tablets showed faster dissolution rates which became slower at higher compaction forces. The increase of the drug content from 30-50% was associated with faster dissolution rates. Similar results were observed for each HME. However, the extruded pre-mixed batches showed slower and more stable dissolution rates. In addition the texture of the compressed tablets was substantially improved showing a gloss finish.

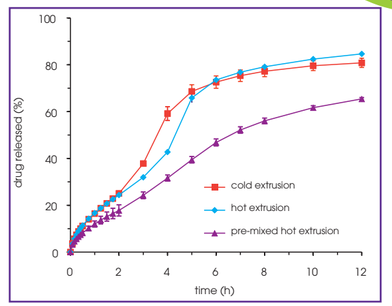

Fig. 3: Dissolution profiles of DfNa/Compritol® 888 ATO (40:60) from lipid matrix tablets (20kN hardness).

Figure 4 illustrates the tablet's aspect after 12h of dissolution. It can be seen that tablets prepared by the hot melt extrusion process (left hand side) disintegrated upon contact with the release medium, which explains increased drug release after 4h (Figure 3).

Extruding the whole tablet formulation (pre-mix + hot extrusion, right hand side) led to improved tablet robustness and thus sustained drug release over at least 12h.

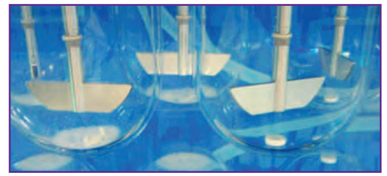

Fig. 4: Photo of dissolution of tablet made by hot extrusion process (left hand side vessel); tablet made by hot extruded + pre-mix process (right hand side vessel) after 12 h dissolution.

CONCLUSION

The current study demonstrated the efficiency of HME to produce solid dispersions of drug/lipid excipient for sustained release at various extrusion conditions at high drug loading. The processing conditions can have an effect on the drug release profile and these can be adjusted along with the tablet properties to provide the desired release patterns.

HME processing with Compritol® 888 ATO can be effectively used to provide sustained drug release of water soluble actives such as DfNa.

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IMPROVING DRUG SAFETY: COMPRITOL® 888 ATO MATRIX TABLETS DELIVER CONSISTENT SUSTAINED DRUG RELEASE IN HYDRO-ALCOHOLIC MEDIA AND WHEN BROKEN

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INTRODUCTION

Bupropion HCl in extended release tablets is prescribed for a number of indications including depression (e.g. Wellbutrin® SR/XL).

Zyban® LP 150 mg, indicated for smoking cessation, contains the same amount of bupropion HCl as Wellbutrin® SR/XL 150 mg. The product label describes serious adverse effect which could arise from accidental faster release of the high drug loaded sustained release dosage form resulting in unintended high plasma concentration.

The label also states that tablets should be taken whole and that splitting could lead to adverse effects. In addition for this particular drug, the FDA recommends the investigation of the effect of alcohol on drug release kinetics.

Compritol® 888 ATO is a glyceryl behenate, with an HLB of 1 and a melting point 70°C. Available as a fine white powder with a mean particle diameter of 50 µm, it is used in tablet processing as lubricant or as lipid matrix former for sustained release. The mechanism of drug release is primarily diffusion through the insoluble, non-swellable matrix [1].

Due to its lipophilic nature and poor wettability, drug release can be successfully extended over prolonged periods of time. Compritol® 888 ATO is an efficient matrix former for freely and highly water soluble drugs; and being resistant to pH changes and insoluble in ethanol, it has been shown to deliver highly robust matrices.

EXPERIMENTAL METHODS

Compritol® 888 ATO based matrix tablets (14 mm) were prepared by direct compression using a single punch excenter press (Korsch EKO3) equipped with flat-faced tooling.

Drug and excipients were blended in a turbula mixer for 5 min and subsequently lubricated with Compritol® 888 ATO.

The formulation is given in Table 1. After manufacturing, tablets were cured for 24h at 50°C in an oven. The tablet hardness was 90 N. Drug release profiles were assessed by dissolution testing in 900 mL demineralised water using the USP II paddle apparatus (37°C, 50 rpm).

Table 1: Composition of tablet formulations process by HME.

Ingredient	% w/w
Bupropion HCl	33.3
Glyceryl behenate	30.3
L-Cystein HCl	2
Dibasic calcium phosphate anhydrate (DCPA)	20.9
Lactose	10.5
Glycerol behenate (lubricant)	3
Total tablet weight	450 mg

RESULTS AND DISCUSSION

Tablets were produced by direct compression of the physical powder blend using a standard tableting machine.

Figure 1 shows that the release retardant properties of the lipidic matrix were comparable to Zyban® LP 150 mg, which comprises a polymer coated hydrophilic matrix.

Drug release from Compritol® matrices was diffusion controlled due the leaching out of water-soluble compounds [2]. The lipid matrix tablet did not swell or erode during dissolution (Figure 3).

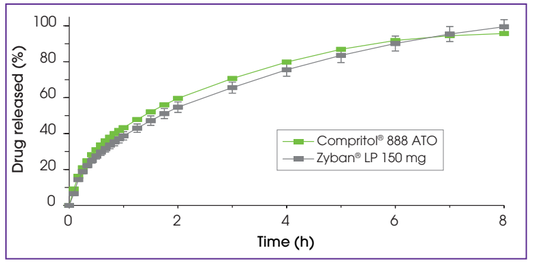

Figure 1: Comparison of bupropion HCl release from Compritol matrix tablets and the market reference Zyban®.

Compritol® sustained release matrices were broken in half and the resulting release curves compared to those from intact tablets (Figure 2). The results show that the lipid matrix tablets maintain their sustained release characteristics *in vitro* minimizing the risk of faster drug release and consequential adverse effects.

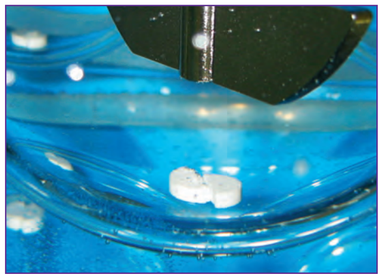

Figure 2: Aspect of the broken Compritol® tablet after 12 h of dissolution.

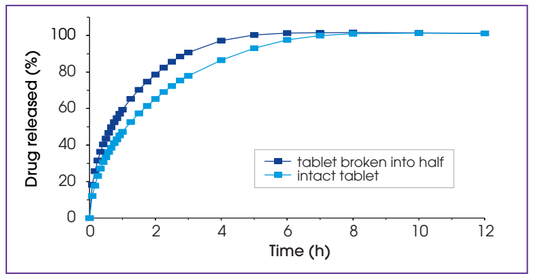

Figure 3: Effect of tablet breakage on *in vitro* bupropion HCl release from tablets consisting of Compritol® 888 ATO.

The FDA recommends dissolution testing of bupropion HCl sustained or controlled release dosage forms in the presence of ethanol over a two hour period to evaluate the possibility of alcohol induced dose dumping. Whole, intact Compritol® SR tablets were tested.

Figure 4 shows the release profiles from intact Compritol® SR matrix tablets in dissolution media of 0.1 M HCl containing 0, 5, 20 or 40% ethanol over a 2 hour period. No evidence of ethanol-induced dose dumping can be observed.

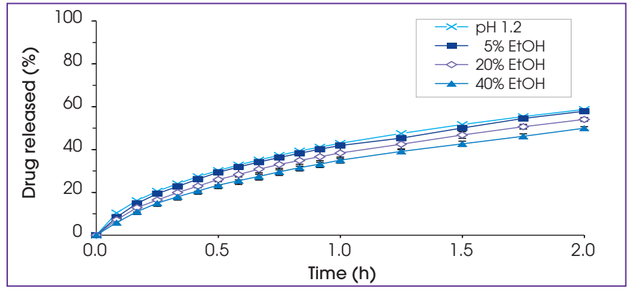

Figure 4: Impact of ethanol in the release medium on bupropion HCl dissolution from Compritol® matrix tablets.

CONCLUSION

Compritol® 888 ATO can be used to produce an effective and robust sustained release matrix tablet by direct compression of the physical powder blend.

Lipid matrix tablets are resistant to the presence of alcohol and show no evidence of altered drug release and dose dumping in case of mis-handling.

Compritol® 888 ATO therefore provides an interesting approach for the production of highly safe, mis-handling, damage and abuse resistant sustained release tablets.

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SUSTAINED-RELEASE OF DICLOFENAC SODIUM FROM WET GRANULATED COMPRITOL® 888 ATO MATRIX TABLETS

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INTRODUCTION

Glyceryl behenate (Compritol® 888 ATO) is a hydrophobic fatty acid ester of glycerol, which has been widely used as a lipophilic matrix-forming agent in the manufacture of sustained-release tablets. When compressed, Compritol® 888 ATO forms an insoluble network structure, allowing dissolution fluid to gradually penetrate and subsequent diffusion-controlled drug release to occur through matrix channels and pores. Drug release from such insoluble matrix systems is mainly dependent on the rate and extent of water permeation and the aqueous solubility of the drug that is embedded in the matrix[1]. Sustained-release matrices comprising Compritol® 888 ATO may be prepared by direct compression, wet granulation or melt granulation methods[2]. Diclofenac sodium is a water-soluble non-steroidal anti-inflammatory drug and the aim of the present study was to investigate the use of wet granulation as a method to produce insoluble matrices using Compritol® 888 ATO for the sustained release of diclofenac sodium.

EXPERIMENTAL METHODS

Formulations comprised; 16.5%w/w diclofenac sodium, 38.5%w/w Compritol® 888 ATO, 28.5% microcrystalline cellulose (Avicel® PH101, FMC BioPolymer, USA) and 28.5% lactose (Pharmatose 200M, DFE Pharma, Germany).
Materials were blended (2C turbula mixer, WAB, Switzerland) for 5 min. Granulation was achieved by the addition of 10% w/v solution of hypromellose (HPMC, Pharmacoat® 603, 606 or 615, Shin-Etsu, Japan) in a planetary mixer (Kenwood Chef®). The wet mass was passed through a 1.7 mm aperture laboratory sieve prior to drying in an oven at 40°C for 24 h and the dry granules were passed through a 1.0 mm aperture laboratory sieve.
The flowability of each batch of granules was determined by measuring the initial and tapped densities and calculating the Carr's index value (%). Dry granules were subsequently blended for 2 min with 1%w/w magnesium stearate prior to compression. The same formulation (without the granulation stages) was directly compressed for comparison.

Tablets (7 mm diameter) were produced at a compression force of 15 kN and a speed of 10 rpm using a Stylcam® 100R rotary press simulator (Medel'Pharm, France) fitted with flat-faced tooling. The weights of ten individual tablets were recorded and tablet strength was measured (Pharmatron 6D tablet tester, Schleuniger, Germany). Drug release profiles were obtained over 12 h (USP apparatus 2, 900 mL water, 37°C) using a Varian 7000 dissolution tester and Cary 50 UV spectrophotometer at 276 nm. Data were analysed for statistical significance ($P < 0.05$) using the Minitab™ software package.

RESULTS AND DISCUSSION

Diclofenac release from Compritol® 888 ATO matrix tablets prepared by direct compression was complete within 1.5 hours (Fig. 1). Diclofenac sodium is a water-soluble drug and despite the relatively high percentage of Compritol® 888 ATO within the formulation, sustained-release was not achieved due to the rapid water permeation through the matrix. Wet granulation of the formulation using different viscosity grades of HPMC as the liquid binder resulted in sustained drug release over a period of several hours (Fig. 1). The presence of the binder within the formulation is thought to increase the tortuosity of the matrix and thus retard water permeation and subsequent drug release through the channels and pores. There was no significant difference ($P = 0.951$) in release rates from the tablets produced by wet granulation using the various grades of HPMC as liquid binder, indicating that the viscosity of the polymer is not an influential factor on drug release.

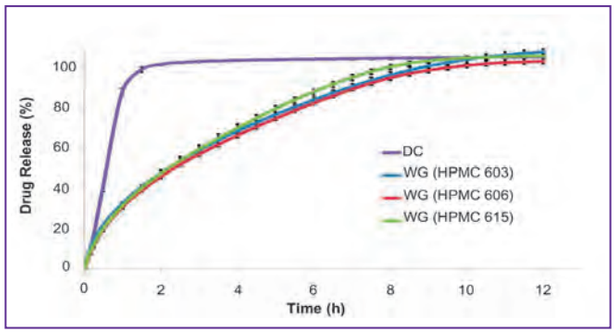

Figure 1: Diclofenac release from Compritol® 888 ATO matrices prepared by direct compression and wet granulation using different liquid binders (mean ± SD, n = 6).

Table 1: Granule flowability, tablet weight uniformity (mean ±SD, n = 10) and tablet strength (mean ±SD, n = 10).

	HPMC 603	HPMC 606	HPMC 615
Carr's Index (%)	19.5	23.9	26.1
Tablet weight (mg)	209 (±1.3)	210 (±2.1)	207 (±2.1)
Tablet strength (MPa)	1.5 (±0.05)	1.57 (±0.06)	1.48 (±0.08)

The flowability of the granules and weight variation of the tablets was inversely related to the viscosity grade of HPMC (Table 1).

The tablets produced from granules comprising HPMC 615 as the liquid binder were significantly weaker ($P = 0.003$) than those comprising the 603 and 606 viscosity grades.

Although this apparent reduction in strength did not significantly affect the overall drug release rate, the marginally faster release rate observed from the tablets comprising HPMC 615 between 4 – 8 hours (Fig. 1) may be ascribed to the weaker matrix structure. Due to the superior flowability of the granules and associated improvement in tablet weight uniformity, the lower HPMC viscosity grade would be preferable when formulating Compritol® 888 ATO matrices using a wet granulation process.

CONCLUSION

Direct compression is not a suitable method for producing matrices for the sustained-release of diclofenac sodium using this particular formulation, even when relatively high levels of Compritol® 888 ATO are employed in the formulation.

Wet granulation using a range of HPMC viscosity grades as the liquid binder proved to be effective in sustaining the release of diclofenac sodium from insoluble matrices.

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DETERMINING DRUG RELEASE FROM COMPRITOL® 888 ATO MATRIX FORMULATIONS

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INTRODUCTION

The development and use of *in vitro* biorelevant dissolution tests is becoming more and more relevant since in depth understanding of the *in vivo* dissolution behaviour of solid dosage forms - being subject to high mechanical stress and food effects throughout gastrointestinal passage - is highly desirable. Biorelevant dissolution tests will eventually be integrated into quality control procedures in formulation development and drug production since it will be essential to assure robust and reproducible oral drug delivery systems in conditions that more closely match the physiological environment.

Such tests may identify unmet needs – and therefore offer opportunities - in terms of excipients, drug delivery and dosage form development.

The objective of this study is to evaluate the robustness of lipid matrix tablets in biorelevant dissolution test systems which simulate passage through the human gastrointestinal (GI) tract. Compritol® 888 ATO (glyceryl dibehenate), the matrix former, is a fine white powder composed of spherical particles with a mean particle diameter of 50µm.

It has excellent tabletting properties and is chemically inert and neutral in flavour. With a low HLB of 1 and a high melting point (70°C) it has proven utility in the production of an insoluble and non-swellable matrix which sustains drug release principally by a mechanism of diffusion [1].

EXPERIMENTAL METHODS

- **Materials**

Theostat® L.P. 100 mg, lot # G00405 (Pierre Fabre Medicament, Boulogne, France) was obtained by prescription, Theophylline, Compritol® 888 ATO, dicalcium phosphate anhydrate (DCPA), lactose monohydrate, silicon dioxide (Aerosil® 200), Mg aluminometasilicate (Neusilin US2) and magnesium stearate used for manufacturing the tablets as well as sodium chloride, hydrochloric acid conc., sodium dihydrogen phosphate, sodium hydroxide and acetic acid used to prepare the release media were all of analytical grade and purchased commercially.

- **Tablet preparation**

For direct compression, 100 mg theophylline, Compritol® 888 ATO and diluents were sieved through a 810 µm mesh, accurately blended and subsequently lubricated and compressed using a single punch excenter press (14 mm, Korsch EK03). The total tablet weight was 600mg.

The solid dispersion was prepared by dispersing theophylline into molten Compritol® 888 ATO. Once cooled, the solid mixture was then calibrated on a 630µm sieve, lubricated and compacted as described above. Table 1 shows the detailed composition of the two tablet formulations.

Ingredient %	DC	SD
Theophylline	16.7	16.5
Compritol® 888 ATO	15	38.5
DCPA	42.9	27
Lactose	21.4	14
Neusilin US2	3	3
Mg stearate	1	1

Table 1: Composition of theophylline matrix tablets containing Compritol® 888 ATO.

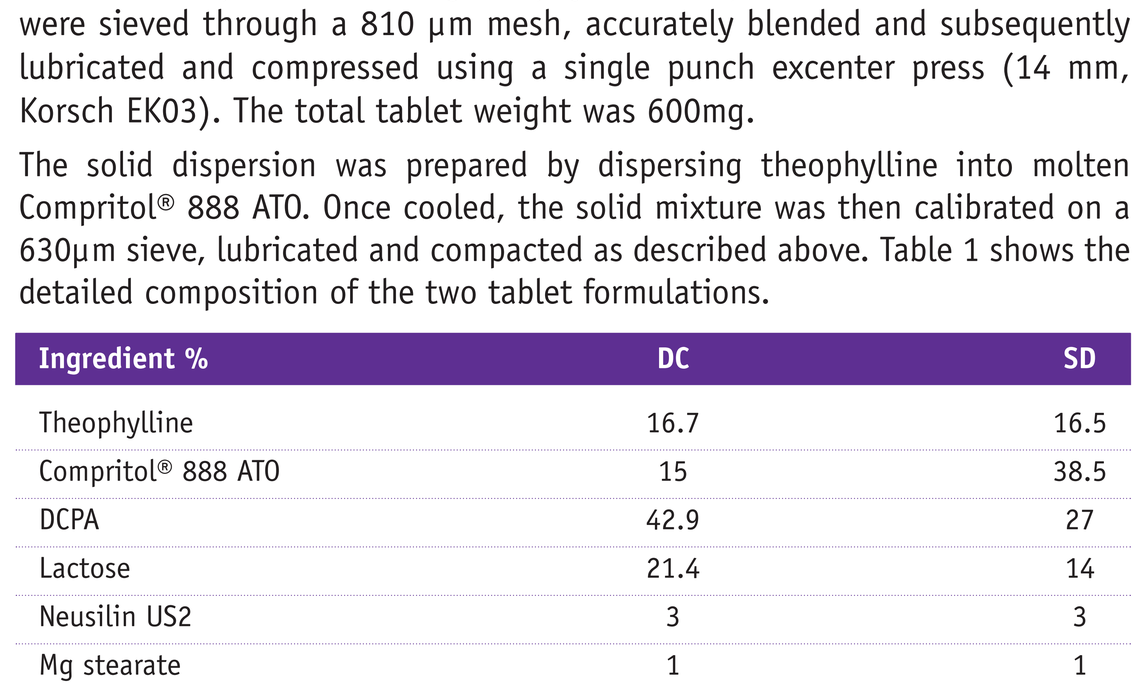

Figure 1: Schematic representations of the USP apparatus III (a), II (b) and the biorelevant stress test apparatus (c) according to Garbacz [3].

GIT	pH	time, min	medium
Stomach	1.8	60	SGFsp
Small intestine	6.8	240	Blank FaSSIF
Proximal colon	5.8	240	SCoF
Colon	6.5	180	Blank FaSSIF

Table 2: Dissolution media [2] and residence times per vessel in the test apparatus.

RESULTS AND DISCUSSION

Compritol® 888 ATO matrix tablets were made by direct compression and from a solid dispersion (see Table 1) and drug release profiles were compared to those of the corresponding HPMC-based market reference Theostat® L.P. 100 mg. Three different dissolution systems were used (i) the standard USP II paddle apparatus filled with a simple phosphate buffer pH 4.5, representing a standard compendial method, and two methods simulating the gastrointestinal passage of the dosage forms: (ii) a simplified pH-gradient method in USP apparatus III to simulate the changing pH-conditions during GI passage and (iii) a biorelevant stress test apparatus with the same set of media but also simulating the biorelevant stresses that can affect the dosage form during GI passage. Fasted State Simulating Gastric Fluid without pepsin (SGFsp), a Blank Fasted State Simulating Intestinal Fluid (Blank FaSSIF) and fluids simulating the pH-environment in the proximal colon (Simulated Colonic Fluid, SCoF and Blank FaSSIF) were used to simulate the pH conditions in the fasting stomach, small intestine and proximal colon (see Table 2 for residence times).

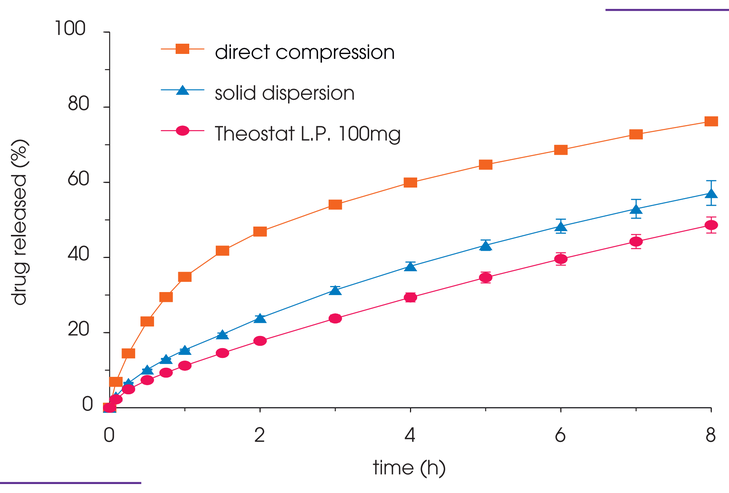

Figure 2: Theophylline release from different tablets obtained with the USP apparatus II and a static pH of 4.5.

Using the USP II apparatus with simple paddle agitation and a static pH, drug release from tablets (n=3) prepared by direct compression was faster compared to tablets made from the solid dispersion (see Fig. 2). This is most likely due to both the difference in the API:lipid ratio (1:1 vs 1:2) (see Table 1) and the denser lipid network created by API diffusion in the Compritol® 888 ATO melt. Drug release of the market reference was well matched by the solid dispersion.

Results from the experiments simulating a fasted gastrointestinal passage of monolithic dosage forms do not show significant differences in product performance. Moreover, they clearly indicate that all the formulations tested are neither sensitive towards the changing pH-conditions (see Fig. 3) nor are significantly affected by biorelevant gastrointestinal stress conditions in the fasted GI tract (see Fig. 4).

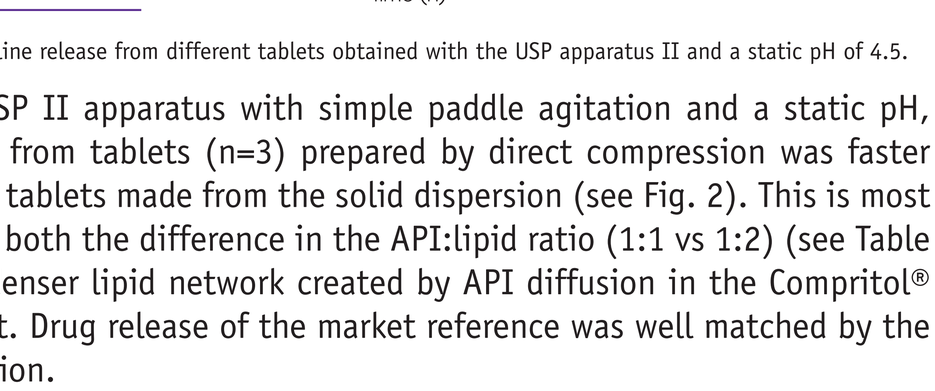

Figure 3: Theophylline release from different tablets under simulated fasted conditions in USP apparatus III.

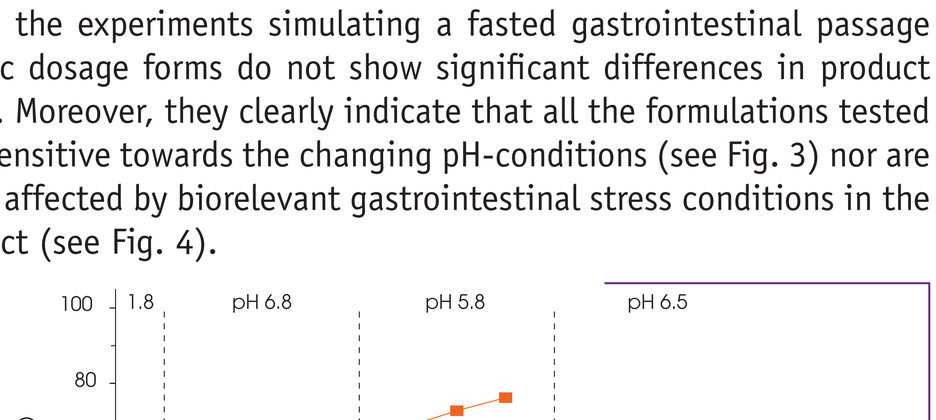

Figure 4: Theophylline release from different tablets under simulated fasted conditions in the biorelevant stress test apparatus.

CONCLUSION

All formulations seem to be quite robust towards changing pH conditions and simulated mechanical stress in the fasted human GIT. It remains to be shown if lipid matrix tablets are robust under fed conditions and avoid food related dose dumping.

ACKNOWLEDGEMENT

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Compritol® 888ATO a release modifier for sustained release of highly water soluble agent: Formulation, Evaluation and IVIVC study

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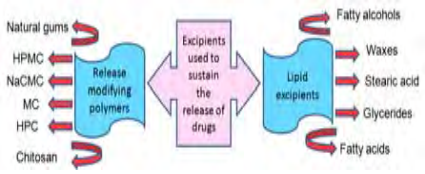
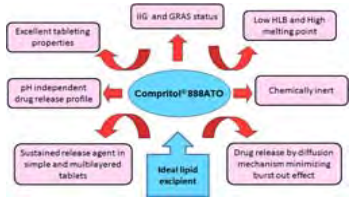
INTRODUCTION

- Development of oral sustained release (SR) tablets for highly water soluble drugs presents a major challenge and opportunity for formulation scientist
- Most of these bioactives if not formulated properly, may be released at a faster rate resulting in exceeding the maximum therapeutic dose and hence will lead to toxic side effects
- Metoprolol succinate (MPL), widely used in the treatment of hypertension, angina pectoris, and arrhythmias, exhibits high water solubility and hence was chosen as a model drug



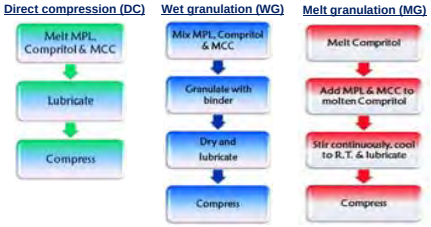


OBJECTIVES

- ✓ **To study Compritol® 888ATO as release retarding matrix in design of SR formulation of MPL**
- ✓ **To evaluate SR formulation of MPL with reference to reliability of release profile, stability and up-scaling**
- ✓ ***In vitro In vivo* correlation (IVIVC) of sustained release MPL tablets (SRMPL)**

EXPERIMENTAL

Preparation methods



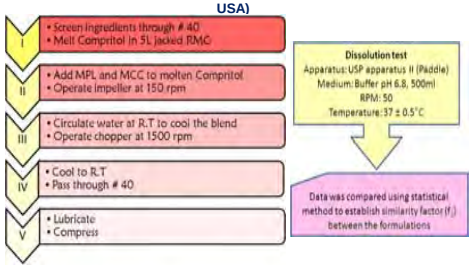
- ❑Compression was carried out on single station tablet press (Unimek, India) with 8.7 mm flat beveled punches
- ❑Effect of amount of compritol, microcrystalline cellulose (MCC), method of preparation (DC, WG & MG), different binders (polyvinyl pyrolidone and L- Hydroxy propyl cellulose), glidants (Aerosil and Neusilin) and additional diluent (Dicalcium phosphate) was studied on MPL release profile

Evaluation

- ❑MPL concentration was quantified using HPLC, UV detector at 274nm
- ❑The tablets were evaluated for weight uniformity, hardness, friability, *in vitro* dissolution and stability (25°C and 40°C) for 3 months
- ❑ **Based on tablet properties and release profile MG method was selected for further development**

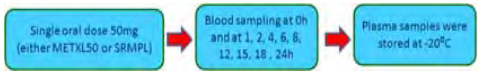
Scale-up study of MPL (SRMPL)

MG was scaled up in 5L of jacketed rapid mixer granulator (Jaguar, USA)

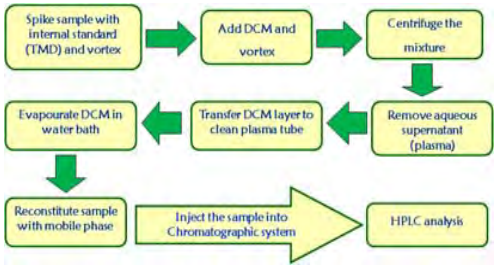


In vivo study in healthy human volunteers

- ✓IVIVC is a rationale relationship between a biological property and a physicochemical property or characteristics of a dosage form
- ✓ Main objective is to minimize the need for *in vivo* studies so that *in vitro* test can serve as surrogate for *in vivo* bioavailability
- ✓ Bioavailability of SRMPL and MetXL50 (commercially available tablets) was studied to establish correlation between the *in vitro* release pattern and *in vivo* findings in 12 healthy human volunteers
- ✓ Randomized, single dose, two-treatment, two period cross-over study design was employed
- ✓ **All the study procedures were performed according to the protocol approved by Institutional ethics committee (EC/Pharm-28/2010)**



Sample preparation



- ➢ HPLC chromatographic system with fluorescence detector (excitation (λex) 216nm and emission wavelength (λem) 312nm)
- ➢ Stationary phase: C_{18} reversed phase column at R.T.
- ➢ Mobile Phase: Mixture of acetonitrile, methanol and phosphate buffer
- ➢ Internal standard: **Tramadol (TMD)**
- ➢ IVIVC correlation was obtained using Wagner-Nelson method

RESULTS AND DISCUSSION

- ➢ MPL: Compritol ® 888 ATO in 1:2 ratio gave desired release profile (Fig. 1)
- ➢ The method used for granulation revealed a significant influence on release profile (Fig. 2)
- ➢ Tablets prepared by melt granulation showed good tablet characteristics (Table 1)
- ➢ No significant change was observed in tablet properties, hardness and release profile by increasing the amount of MCC or by using additional diluent, different binders and glidants
- ➢ Curing procedure did not have influence on release profile.
- ➢ **Melt granulation step of SRMPL was scaled up successfully**
- ➢ SRMPL retarded MPL release and no significant difference (f_2 >50) was observed in dissolution profiles of SRMPL and Met XL 50 (Fig. 3)
- ➢ The SRMPL showed good stability with respect to release during the storage period (Fig. 4)

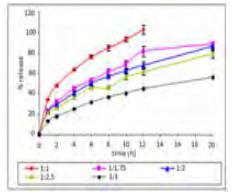


Fig. 1: Effect of amount of compritol®888 ATO on MPL release

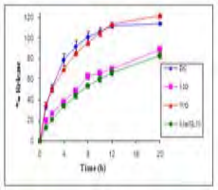


Fig. 2: Release profiles of MetXL50 and MPL tablets prepared by DC, MG and WG

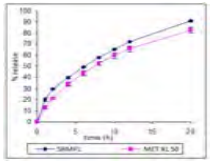


Fig. 3: Comparative dissolution profile of SRMPL with Met XL50

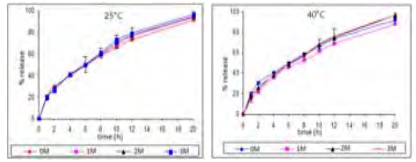


Fig. 4: Dissolution profile of SRMPL stability batches

Parameter	SRMPL
Drug content	93.62 ± 0.07%
Weight uniformity	174.6 ± 5.9
Hardness	2.0-2.5 kg/cm²
Friability	0.57 %
% drug release *in vitro* after 20h	91.35± 0.89%

Table 1: Tablet properties

- ➢ HPLC chromatographic method was successfully validated by analysis of human plasma prepared at concentrations spanning the calibration range (Table 2)
- ➢ The plasma concentration time profile of SRMPL and MetXL50 was comparable (Fig. 5)
- ➢ The average Cmax, Tmax and Cumulative AUC of SRMPL and METXL50 tablets in 12 volunteers is shown in Table 3

HPLC method		
Good chromatographic separation		
Recovery of extraction	More than 90%	
Limit of quantitation	5ng/ml	
Average retention time	MPL 30.14 mins	TMD 25.78 mins
Linearity	10-200 ng/ml	R^2 0.997

Table 2: HPLC analysis

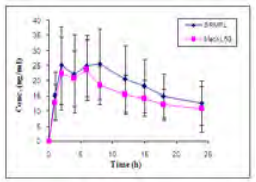


Fig. 5: Mean ± S. D. plasma concentration time profiles of SRMPL and MetXL50

Parameter	SRMPL	MetXL 50
C_{max}	30.97± 11.87 ng/ml	29.90 ± 11.07 ng/ml
T_{max}	4.33 ± 2.28 h	5.16 ± 1.90h
Cumulative AUC	454.96 ± 193.82ng.h/ml	372.67 ± 128.22 ng.h/ml

Table 3: Mean Cmax, Tmax and Cumulative AUC of SRMPL and MetXL50

- ✓ IVIVC in the present study was generated using pooled mean fraction of dose dissolved *in vitro* (FRD) and pooled mean fraction of dose absorbed *in vivo* (FRA) for SRMPL and MetXL50 (Fig. 6)
- ✓ **R^2 values indicated excellent correlation**

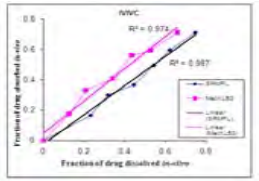


Fig. 6: Fraction of drug dissolved *in vitro* vs. fraction of drug absorbed *in vivo* for SRMPL and MetXL50

CONCLUSIONS

- ❖ **SRMPL tablets were successfully formulated by melt granulation method using Compritol®888ATO as release modifier**
- ❖ **The average cumulative AUC values of SRMPL and MetXL50 were found to be comparable**
- ❖ **High correlation values obtained from graphs of percent drug dissolved *in vitro* vs. percent drug absorbed *in vivo* for SRMPL as well as MetXL50 indicated excellent IVIVC**

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- ➢ **M K Rangnekar labs, Mumbai, India**
- ➢ **Indian Council of Medical Research**

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38th Annual Meeting and Exposition of The Controlled Release Society,2011,Maryland,USA

Formulation Effects on Drug Release from Sustained-Release Compritol® 888 ATO Tablets & Mini-Tablets

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Introduction

Although most medicinal products are developed as solid oral dosage forms, the significant anatomical differences of the buccal cavity within paediatric and adult patients mean that children, particularly those under 5 years of age, encounter swallowing difficulties[1]. Mini-tablets are a potential dosage form suitable for paediatric drug delivery and can be produced via traditional tableting methods, such as direct compression. Sustained-release mini-tablets may offer distinct advantages over many conventional dosage forms used in paediatric medicine. In addition to their small size, which helps to overcome issues associated with dysphagia, they may be designed to mask unpleasant tastes to improve palatability whilst also modifying the release of the active drug substance from the formulation. Compritol® 888 ATO (glyceryl behenate) is commonly used in formulating sustained-release lipid matrices[2]. When compressed, Compritol® 888 ATO forms an insoluble network structure, allowing water to penetrate and subsequent drug release to occur via diffusion. In a previous study, the effect of various diluents and the compaction force used during manufacture on drug release from Compritol® 888 ATO tablets were reported[3]. The aim of the present study was to assess the effects of various diluents on drug release from Compritol® 888 ATO tablets and mini-tablets of different sizes.

Materials & Methods

Formulations comprised; 16.7 %w/w anhydrous theophylline, 15 or 25 %w/w Compritol® 888 ATO (Gattefossé, France) 3 %w/w, magnesium alumino silicate (Neusilin® US2, Fuji Chemical, Japan), 1 %w/w magnesium stearate (Sigma Aldrich, France) and 64.3 or 54.3 %w/w diluents (either; Microcrystalline cellulose (MCC, Avicel® PH101, FMC Biopolymer, Belgium), Lactose (Lactopress® spray dried, Domo, Netherlands), dibasic calcium phosphate anhydrous (DCPA, Fujicalin®, Fuji Chemical, Japan) or DCPA and lactose (2:1). Materials were blended for 2 min (46 rpm) and subsequently for 1 min (96 rpm) with lubricant (2C turbula mixer, WAB, Switzerland). Compression was performed using a using a Stylcam® 100R rotary press simulator (Medel'Pharm, France) at a production rate of 20 rpm. Tablets (12 mm diameter, 600 mg) were produced at a force of 20 kN, whilst mini-tablets (2mm (7 mg), 3 mm (15 mg) and 4 mm (25 mg)) were produced at forces of 1, 3 and 6 kN respectively. Tablet strength was measured (6D tablet tester, Schleuniger, Germany) and 12 h drug release profiles obtained (USP apparatus 2, phosphate buffer pH 4.5, 37°C) using a Sotax AT7 dissolution bath and an Agilent 8453 DAD Spectrophotometer at 271 nm. Data were analysed for statistical significance ($P < 0.05$) using the Minitab™ software package.

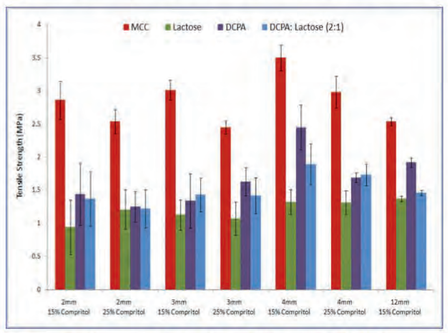

Fig. 1. Tensile strength of Compritol® 888 ATO tablets and mini-tablets produced with various diluents (mean ± SD, n = 10)

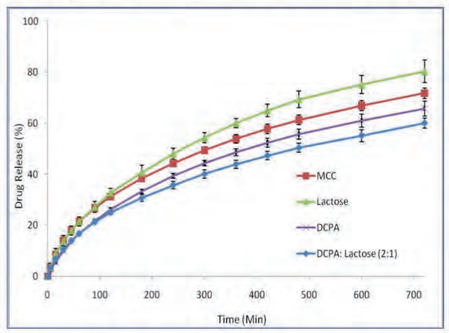

Fig. 2 Theophylline release from 12 mm tablets comprising 15 %w/w Compritol® 888 ATO with various diluents (mean ± SD, n = 6)

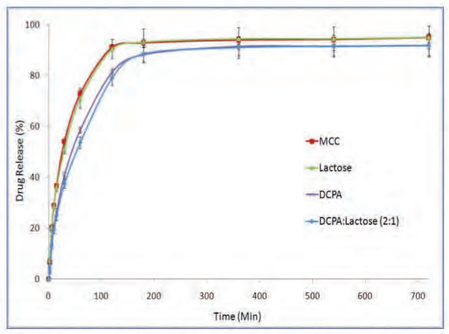

Fig. 3. Theophylline release from 2 mm mini-tablets comprising 15 %w/w Compritol® 888 ATO with various diluents (mean ± SD, n = 6)

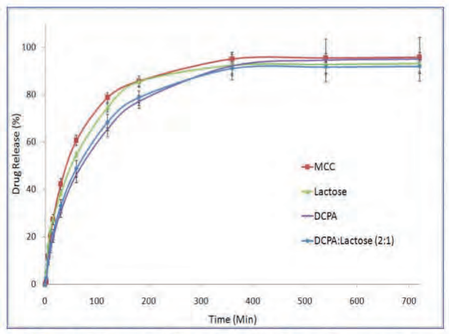

Fig. 4. Theophylline release from 2 mm mini-tablets comprising 25 %w/w Compritol® 888 ATO with various diluents (mean ± SD, n = 6)

Results & Discussion

Robust tablets and mini-tablets were obtained from all formulations (Fig 1) tablet and mini-tablet strength was significantly higher in tablets containing MCC due to its compressibility properties. Drug release from 12 mm tablets comprising 15 %w/w Compritol® 888 ATO was sustained over 12 h (Fig 2). Significantly faster release was achieved from tablets with lactose, presumably due to the solubility of the diluent increasing solvent penetration of the matrix, and from the tablets with MCC. The latter structures were observed to swell and split laterally during dissolution testing due to MCC promoting disintegration. Drug release from mini-tablets with 15 %w/w Compritol® 888 ATO was more rapid in comparison to the 12 mm tablets (Figs. 3, 5 & 7). The same diluent effect trends were seen with mini-tablets, with significantly faster release occurring from tablets containing lactose or MCC. Release from mini-tablets was retarded further by increasing the Compritol® 888 ATO level to 25 %w/w (Figs 4, 6 & 8), whilst the slowest and most consistent release rates were obtained from the formulations comprising the insoluble DCPA as diluent, alone or in combination with lactose. Release rates decreased as mini-tablet size increased (2 mm > 3 mm > 4mm) due to the shorter diffusion pathways. Results indicate that higher concentrations of Compritol® 888 ATO are required to sustain drug release from mini-tablets and that the solubility of the diluent(s) play a key role in modifying release rates.

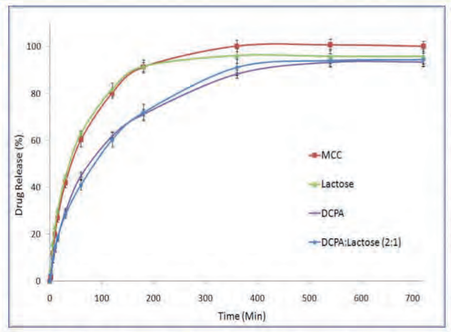

Fig. 5. Theophylline release from 3 mm mini-tablets comprising 15 %w/w Compritol® 888 ATO with various diluents (mean ± SD, n = 6)

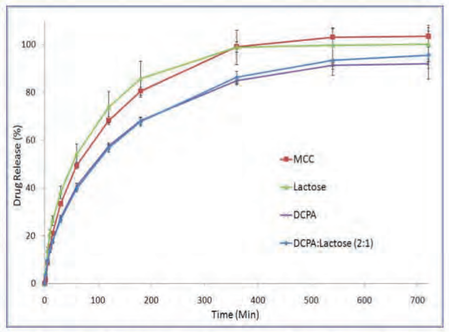

Fig. 6. Theophylline release from 3 mm mini-tablets comprising 25 %w/w Compritol® 888 ATO with various diluents (mean ± SD, n = 6)

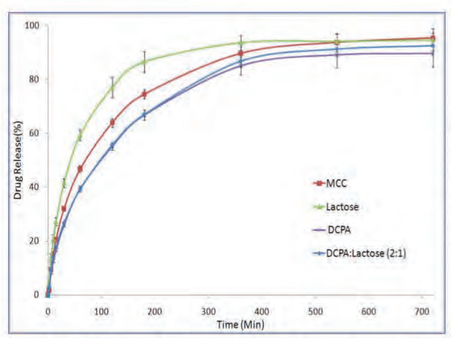

Fig. 7. Theophylline release from 4 mm mini-tablets comprising 15 %w/w Compritol® 888 ATO with various diluents (mean ± SD, n = 6)

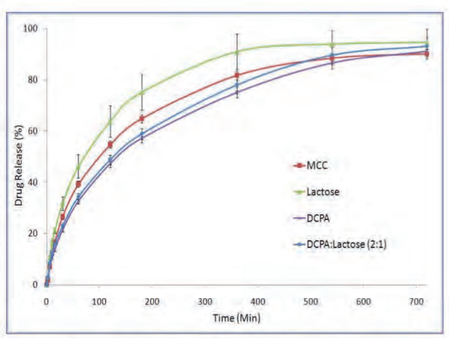

Fig. 8. Theophylline release from 4 mm mini-tablets comprising 25 %w/w Compritol® 888 ATO with various diluents (mean ± SD, n = 6)

Conclusions

Although a relatively low concentration of Compritol® 888 ATO is sufficient to sustain drug release from matrix tablets over a prolonged period, drug release is significantly faster from mini-tablets. The choice of diluents(s) also effects the release profiles obtained, with MCC and lactose likely to increase the rate of solvent penetration. Further studies are warranted to explore the development of sustained-release mini-tablets using lipid matrix formulations.

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Performance of a Compritol® 888 ATO Lipid Matrix Tablet to Deliver Sustained Release of Diclofenac Sodium

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INTRODUCTION

Diclofenac sodium is a non-steroidal anti-inflammatory agent (NSAID) with antipyretic and analgesic actions. Diclofenac is used to treat pain, dysmenorrhea, ocular inflammation, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and actinic keratosis. It is a highly water soluble salt (50 mg/mL).

Compritol® 888 ATO is a glyceryl behenate, with an HLB of 1 and a melting point 70°C. Available as a fine white powder with a mean particle diameter of 50µm, it is used in tablet processing as a lubricant or as a lipid matrix former for sustained release. The mechanism of drug release is primarily diffusion through the insoluble, non-swellable matrix [1].

Compritol® 888 ATO lipid matrix tablets can be made using straightforward methods. Depending on the properties of the active pharmaceutical ingredient (API), direct compression (DC) / wet granulation (WG) can produce stable sustained drug release.

For highly water soluble APIs other simple processing methods are of interest, including solid dispersion [3], melt extrusion and melt granulation. These processes require an additional step where the drug is dispersed in to molten Compritol® 888 ATO and once cooled the solid dispersion is ground to obtain granules for compression.

The objective of this study is to evaluate the effect of tablet processing methods on Compritol® 888 ATO lipid matrix tablets containing diclofenac sodium.

EXPERIMENTAL METHODS

Compritol® 888 ATO is a Glyceryl behenate NF, synthesized by esterification of behenic acid (C22) and glycerol and therefore consists of a mixture of mono, di and tribehenate of glycerol, the diester fraction being predominant.

All tablets contained 100mg of Diclofenac sodium (provided by Sochibo). The amount of Compritol® 888 ATO varied subject to formulation and processing methods. Diluents included lactose and anhydrous dicalcium phosphate with magnesium stearate providing lubrication.

For direct compression, excipients and API were firstly blended together, followed by addition of the lubricant to the external phase in a second blending step. Sintering treatment on the tablets was carried out at 80°C for 30 minutes in dry heat conditions.

Solid dispersions were prepared by dispersing diclofenac sodium in to molten Compritol® 888. Once cooled the solid mixture was then ground on an oscillant screen. The powder obtained was calibrated on a 630µm sieve; additional tablet ingredients were blended prior to direct compression. All tablets were prepared on an alternative tabletting machine (Korsch Ek03).

The contact angle of tablet surface was measured using a goniometer ILMS from GBX instruments. Drug release profiles were assessed by dissolution testing equipped with UV measurement. All stability tests were performed under ICH conditions.

RESULTS AND DISCUSSION

Direct compression of diclofenac sodium with Compritol® 888 ATO produced tablets with good physical characteristics. However, sustained release could not be achieved even with the use of 50% Compritol® 888 ATO by weight in the formulation. The density of the Compritol® 888 matrix is not sufficient to maintain the drug entrapped when exposed to aqueous solution.

Graph 1 shows the drug release from a tablet made by direct compression with 38.5% of Compritol® 888 ATO, 16.5% of diclofenac sodium (diluents being the remaining ingredients). Diclofenac sodium was completely released after 30 minutes.

The application of a sintering process on tablets made by DC (herewith referred to as DC-S) appears to affect the structure of the lipid matrix resulting in a denser formation. Porosity data before and after sintering confirm this postulation. The repartition of Compritol® 888 ATO is also slightly different and a lipid layer is observed at the surface of the tablet.

To study the effect of heat treatment on lipid matrix tablets, tablets were produced using Compritol® 888 ATO powder dyed blue (figures 1 and 2).

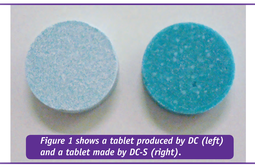
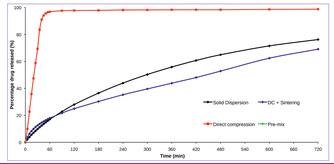


Figure 1 shows a tablet produced by DC (left) and a tablet made by DC-S (right).

Figure 2 shows the cross sectional view of tablets made by DC (right) and DC-S (left).

The process of DC appears to yield an even repartition of Compritol® 888 ATO throughout the matrix and blue particles are visible across the entire tablet surface. A distinct difference in aspect can be seen in the sintered tablet (DC-S); the blue coloration is much darker indicating that the Compritol(R) 888 ATO has melted into the tablet interstices and other ingredients. The cross-sectional view of the tablets (figure 2) shows that Compritol® 888 ATO is distributed homogenously throughout both the DC and DC-S tablets, with the effect of sintering and the melting of the Compritol® 888 ATO producing a much darker coloration throughout the tablet.

Dissolution results for DC-S tablets illustrate the differences in the retardant properties of lipid matrix tablets produced by DC, DC-S and solid dispersion (SD). **These results suggest that sintering may decrease the porosity of the matrix, increasing its retardant capacity resulting in a sustained drug release over 12 hours (see graph 1).**



Graph 1. Percentage drug release from Compritol® 888 ATO matrix tablets made by DC, DC-S and SD.

Solid dispersion is also an effective method to produce a lipid matrix for sustained drug release. Diclofenac sodium was dispersed into molten Compritol® with a ratio 30/70 w/w. After cooling the solid dispersion is ground into a powder, blended with diluents, lubricant and compressed. The tablets contained 38.5% of Compritol® 888, 16.5% of diclofenac sodium and the remaining ingredients were diluents. Again tablets were made with blue Compritol® 888 ATO to evaluate the characteristics of the matrix.

The Compritol in SD tablets is a much darker blue indicative of the melting process. The blue zones appear larger and well-distributed throughout the tablet (figure 3).

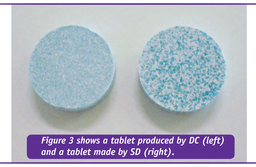


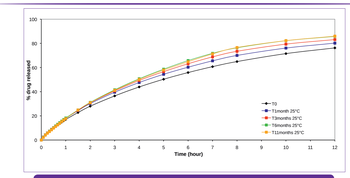
Figure 3 shows a tablet produced by DC (left) and a tablet made by SD (right).

The drug release profile from SD tablets (Graph 1) indicates that the process of dispersing API into molten excipient enables the production of a matrix with good release retardant properties.

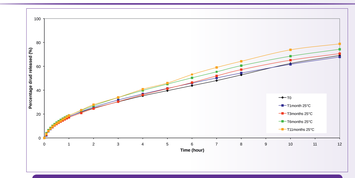
To further evaluate the effect of processing methods on tablet characteristics the contact angle of the tablets' surface was measured. The results signify the wettability of the tablet surface (figure 4).

Figure 4 Contact angle for tablets made by DC, DC-S and SD.

Tablets made by DC have the lowest contact angle, 94.1° indicating a greater wettability of the tablet surface compared to DC-S and SD tablets. Solid dispersion increases the surface contact angle to 102.6°, reducing the wettability and increasing the retardant properties of the tablet structure. The sintering treatment produces the highest surface contact angle, 121.8° suggesting the lowest wettability, which confers with the dissolution results.
Graphs 2 and 3 show the results of stability studies for SD tablets and DC-S tablets respectively, indicating stable drug release profiles at (25°C) during 12 months.



Graph 2. Diclofenac sodium-Compritol® 888 ATO tablets produced by SD.



Graph 3. Diclofenac sodium-Compritol® 888 ATO tablets produced by DC-S.

CONCLUSION

Compritol® 888 ATO is a functional excipient that has proven utility for the production of hydrophobic, non-swellable matrix tablets for sustained drug release.

As with all functional excipients, the nature of the API, its water solubility and the dose all influence the choice of formulation approaches with Compritol® 888 ATO. Direct compression can be sufficient for low dose tablets and APIs with medium water solubility. For highly water soluble APIs, like diclofenac sodium, it is important to decrease the porosity of the tablet, generating a denser lipid matrix to sustain the release in aqueous solution. This can be achieved by using straightforward techniques such as solid dispersion or by applying a post-tableting heat treatment such as sintering.

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