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Smart strategies for sustained release tablets: *Compritol® 888 ATO*

An essential excipient for modulating drug release

Lipid excipients can be utilized to deliver clinically relevant sustained drug release profiles (8, 12, 24 hours) through the creation of an insoluble matrix structure from which diffusion is the principal drug release mechanism [1].

Compritol® 888 ATO (glyceryl dibehenate EP/NF) is a lipidic excipient with GRAS status, available as a powder, with a wide range of processing options for the production of sustained release tablets.

Used as a sustained release agent worldwide, it forms a robust lipid matrix following both tablet compression and when used in melt processes. It is an excellent alternative to other release retarding excipients, offering a combination of formulation, biopharmaceutical and manufacturing advantages, including:

* Low percolation threshold
* Chemically inert
* Insoluble in hydro-alcoholic media
* Use in direct compression, granulation, spray coating and extrusion

Here we describe the physical and chemical characteristics of Compritol® 888 ATO and critical formulation attributes to design a sustained release tablet through our case studies with water-soluble drugs.

Click here to register for our live webinar on June 4, 2014 : Addressing Biopharmaceutical Adversities: Sustained Release Lipid Matrices

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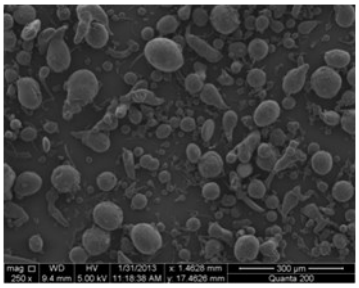

Figure 1. SEM image of Compritol® 888 ATO

Physical and chemical characteristics of Compritol®888 ATO (glyceryl dibehenate EP/NF)

* Well-defined composition of mono, di and triglycerides of C22 behenic acid
* White fine powder
* Particles of 50 µm and spherical shape (see Fig.1)
* Neutral in taste and flavor
* Chemically stable and inert
* Melting range 68.5 – 71.5°C

In addition, Gattefossé has extensive batch-to-batch reproducibility data and QbD study documentation.

The specific chemical composition of Compritol® 888 ATO delivers distinct ***biopharmaceutical advantages*** when used as a sustained release agent.

Globally acceptable excipent.

Compritol® 888 ATO is supplied as a ready-to-use powder for the formulation of SR matrix tablets.

It is well-characterized with USA Type IV DMF, GRAS, numerous FDA IIG listings and global approvals (USA, Japan, PR China).

It provides broad scope for the development of proprietary drug delivery systems.

Drug release mechanism from Compritol® 888 ATO matrix

Drug release from sustained release tablets made with Compritol® 888 - as the only release retarding excipient - is diffusion controlled and not driven by swelling and erosion (see Fig. 2).

This facilitates simple product design, including ease of drug release modulation and high reproducibility.

Drug release prediction can be easily applied to Compritol® 888 matrix tablets because diffusion is the principle drug release mechanism.

Application of mathematical prediction has the potential to reduce experimental ressources, hence, drug development time and costs [2].

Figure 2. Compritol® 888 matrix tablet before and after 12h dissolution

Formulation critical attributes

Designing a lipid matrix is straightforward but it is necessary to understand the main factors that influence drug release:

The choice of diluent(s) is crucial to the matrix design since they enable the formation of pores through which drug and aqueous solution diffuse, thereby influencing the drug release profile.

Typically in direct compression, **15-20 % of Compritol® 888** creates an infinite matrix network, resulting in robust and reproducible SR tablets. However, drug diffusion is highly dependent on the hydrophilicity and amount of other formulation ingredients used; mainly API and diluents. For this reason, it is sometimes necessary to increase the concentration of Compritol® 888 to achieve the target release kinetics.

Formulation insight

In compression, the drug to lipid to diluents ratio(s) and type of diluents are the main factors to be taken into account.

In diffusion driven drug release, the dimensions of the dosage form/device influence drug release rate.

Clinically relevant SR profiles with low Compritol 888 concentration

Table 1. 100 mg theophylline tablet with Compritol® 888 ATO matrix

INGREDIENTS, %W/W	A	B	C	D	E	F
Theophylline	20	20	20	20	20	20
Compritol® 888 ATO	5	10	15	20	30	40
DCPA (Fujicalin SG)	37.25	34.75	32.25	29.75	24.75	19.75
Lactose (Flowlac 100)	37.25	34.75	32.25	29.75	24.75	19.75
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5

Table1 shows theophylline tablet formulations with increasing concentration of Compritol® 888 ATO and decreasing diluents. The final tablet weight was 500mg and diameter 12mm.

In direct compression and wet granulation 15—20 % Compritol® 888 ATO is frequently the recommended concentration to begin formulation development.

At high lipid concentrations (30-40% Compritol® 888) the entire drug dose was recovered only after 72 hrs (Fig 3B)

If the addition of higher lipid concentrations is undesired or impractical, the formulation of freely soluble molecules is possibly by varying drug dose, diluent type and/or tablet dimension.

All Compritol® 888 concentrations above 5% provide prolonged theophylline release over at least 12h (Fig.3A).

Drug release rates were slower with decreasing diluent concentration and increasing Compritol® 888 due to enhanced lipophilicity of the matrix and reduced pore formation.

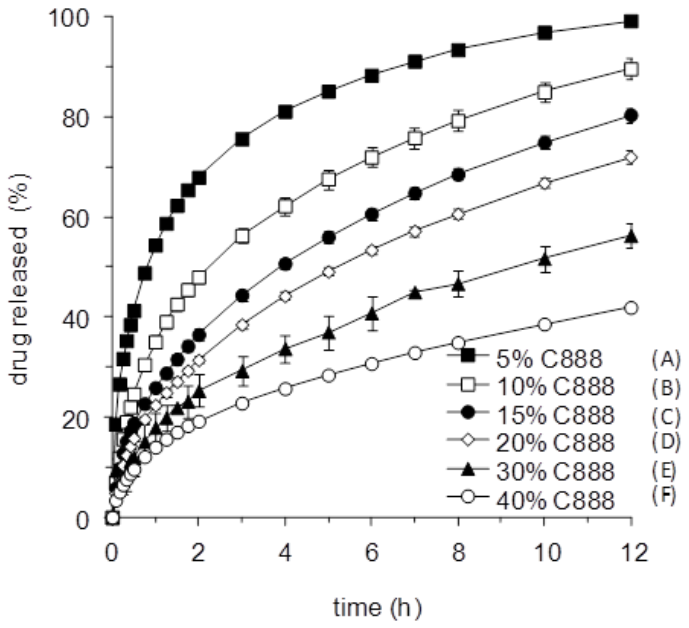

Figure 3A. Theophylline release from SR tablets made by direct compression with varying Compritol® 888 concentrations.

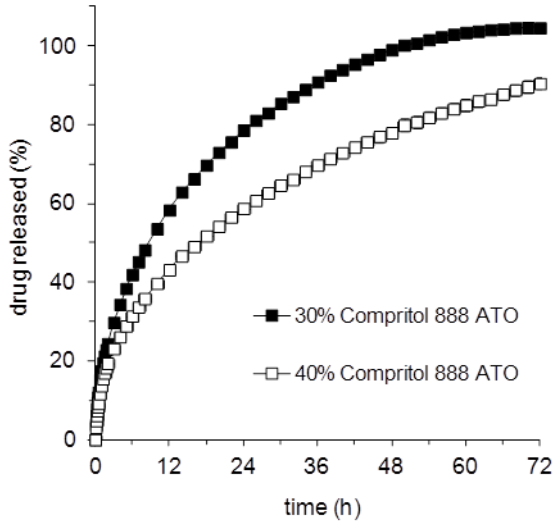

Figure 3B. Theophylline release over 72 hours from SR tablets made by direct compression with 30/40% Compritol® 888 concentration.

If drug dose is very high and a limited amount of Compritol® 888 must be used then selecting the right diluent is key to obtaining the desired release profile.

The modification of tablet diameter/height provides an additional approach to modulate drug release due to the effect on specific surface area and diffusion.

Compritol® 888 ATO can provide effective SR properties in mini-tablets (3mm—4mm diameter)[3].

Compritol® 888 can be used in numerous manufacturing processes for oral solid dosage forms, providing formulation flexibility and scope for innovation.

Process flexibility: scope for both simplicity and innovation

Cold process such as direct compression (DC) is straightforward producing drug release profiles similar to wet granulation (WG). Wet granulation also works well with the addition of a low concentration of binder and provides superior tablets characteristics compared to direct compression.

Alternatively, there are several hot melt techniques available. Melt processes have the advantage of providing significantly slower drug release rates due to drug entrapment in the lipid. Hot Melt Extrusion (HME) with Compritol® 888 is particularly interesting because extrusion can be performed at low temperatures (70°C) and the use of plasticizers can be avoided.

With process flexibility, formulating SR dosage forms with Compritol®888 is straightforward with many options for equipment, API properties and target dosage form.

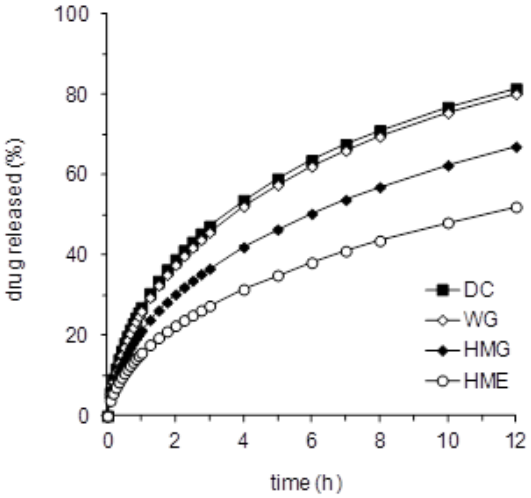

Figure 4: Effect of preparation method on niacin release.

Processing techniques influence the release retarding properties of lipid matrices.

Figure 4 shows the effect of processing for the same formulation with Niacin as water soluble model drug (cs = 27mg/mL).

Processing advantages of Compritol® 888 ATO

The broad processing flexibility of Compritol® 888 ATO enables formulation simplification, provides solutions for challenging formulations and options for the development of innovative drug delivery systems:

* ***In DC: high reproducibility and low variation with Compritol® 888 concentration <30%***
* ***In WG: no swelling, gelification or lumping and simple cleaning***
* ***In HME: low temperatures, no plasticizer, high drug load (up to 75%)***
* ***In hot melt granulation: high drug load, no drying, no solvents.***

Biopharmaceutical advantages of Compritol® 888 ATO

* Demonstrable *in vitro / in vivo* correlation of sustained drug release [4]
* Lipid matrices resistant to physiological conditions and hydroalcoholic conditions
* Non-digestible and non-toxic
* Lipid matrix by melt process can be abuse resistant

References

[1] Barakat, N. S., Elbagory, I. M. and Almurshedi A. S. **Formulation, release characteristics and bioavailability study of oral monolithic matrix tablets containing carbamazepine.** AAPS PharmSciTech. 9.3 : 931-38, 2008

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[3] Roberts M., Vellucci D., Mostafa, S., Miolane C, and Marchaud D. 2012. **Development and evaluation of sustained-release Compritol 888 ATO matrix mini-tablets**. Drug Dev Ind Pharm. Sep;38(9):1068-76.

[4] Patere S., Desai N., Jain A., Kadam P., Thatte U., Gogtay N., Kapadia C.; Farah N.; Nagarsenker M. **Compritol® 888 ATO a lipid excipient for sustained release of highly water soluble active: formulation, scale-up and IVIVC study**. Current Drug Delivery 10 548-56, 2013.

To receive a full version of our recently published **Formulation Guidelines for Sustained Release Tablets** please contact your local Gattefossé representative (www.gattefosse.com)

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