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.

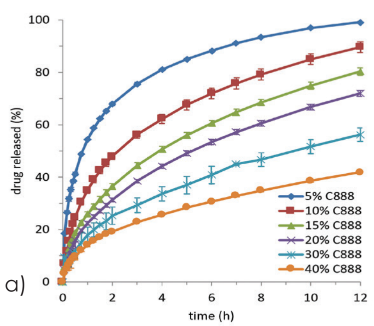
Equation 1 $$\frac{M_t}{M_\infty} = k \cdot t^n$$

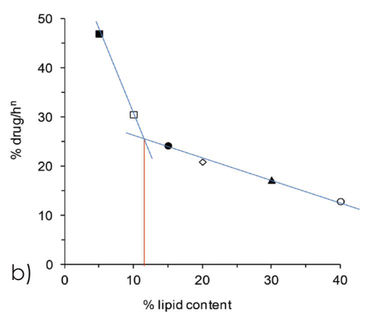
Equation 2 $$\frac{M_t}{M_\infty} = 4 \cdot \sqrt{\frac{D \cdot t}{\pi \cdot R^2}} - \frac{D \cdot t}{R^2}$$

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.

a) 

b) 

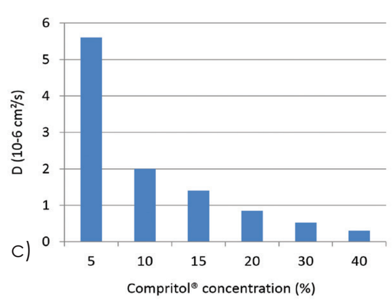
c) 

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).

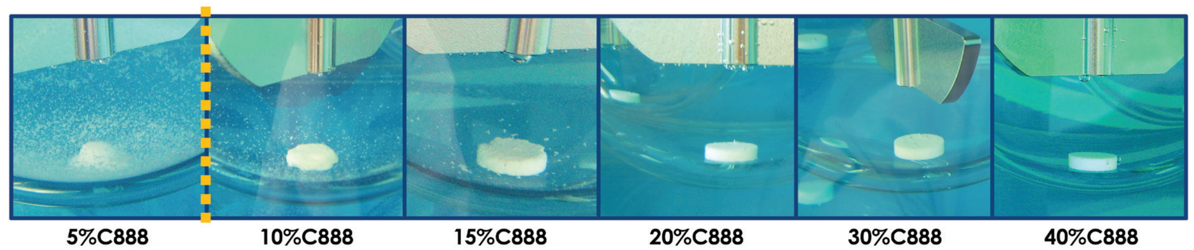


Figure 2: Tablet aspect after 12h of dissolution for different Compritol® 888 concentrations.

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.

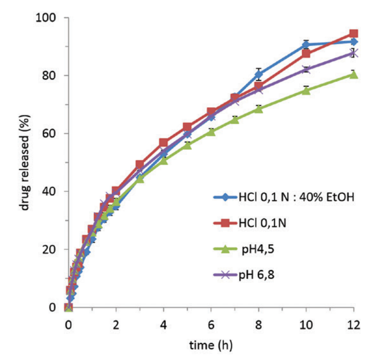


Figure 3: Effect of pH changes and the presence of ethanol on drug release.

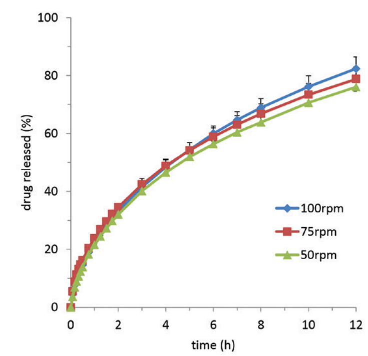


Figure 4: Effect of dissolution paddle speed on drug release.

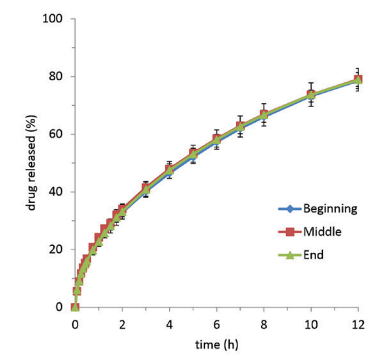


Figure 5: Theophylline release from tablets taken at different production time points.

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.

6 – REFERENCES

[1] Millan M. et al., Pharm. Res. 15 (2) (1998) 220–224
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[3] Caraballo I.. et al. Int. J. Pharm. 1999; 181:23-30.
[4] Fuertes I. et al. Eur J Pharm Biopharm. 2006; 64:336-42