Streamlining the Design of Sustained Release Matrix Tablets Using Mathematical Modeling For Drug Release Optimization

Y. Rosiaux, F. Desvignes, JM. Girard, C. Miolane, S. Hughes and D. Marchaud

Gattefossé GSAS, 36 chemin de Genas, 69804 Saint-Priest, France
yrosiaux@gattefosse.com

ABSTRACT SUMMARY

Drug release from Compritol® 888 sustained release (SR) matrix tablets is diffusion controlled and not driven by swelling and erosion. This facilitates simple product design, where drug release prediction can be easily applied to Compritol® 888 matrix tablets with a simplified fick’s law diffusion equation.

To start, the minimum amount of Compritol®888 needed to obtain a non-erodable matrix in theophylline tablets has been assessed by screening various tablets in a disintegration test. When tablets successfully passed this test then drug release is evaluated in dissolution. The formulation can then be optimized for drug release by applying a mathematical model. This approach has been found to be an efficient way to define the minimum quantity of Compritol®888 required to construct a robust SR matrix.

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. Otherwise geometric changes of the device can induce changes in the drug release mechanism (e.g. erosion)\(^1\).

Therelease 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.

EXPERIMENTAL METHODS

Tablet preparation

500mg 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 12mm 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 profile from tablets was determined using the USP method. Drug is released by diffusion, therefore the simplified Equation 1 of Fick’s 2\(^{nd}\) law of diffusion has been applied:

$$\frac{M(t)}{M(\infty)} = 1 - \frac{D \cdot t}{R^2}$$

where \(M(t)/M(\infty)\) 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 kinetic for other drug/lipid concentrations.

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

\[ D_{\text{20\%C888/20\%theo}} = 1.36 \times 10^{-6} \]

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 curve and corresponding D values for 20% and 40% of Compritol®888.

These known D values could then be correlated to the respective theophylline concentration. Once the best correlation curve is obtained (R² close to 1), the D value for other theophylline/Compritol®888 concentrations can be predicted without any further experiments and drug release from tablets with varying Compritol®888 concentrations calculated 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 curves). After prediction tablets with these concentrations have been prepared and subsequently released to confirm the predictions (Figure 4 symbols). As it can be seen theory and reality were in good agreement. Alternatively, the effect of different drug concentrations on release kinetics can be predicted (data not shown).

CONCLUSION

A rapid screening using a disintegration test enables the minimum amount of Compritol®888 in theophylline SR 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.

REFERENCES