Experimental measurements and mathematical modelling of volatile loss from binary solvent systems

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PURPOSE

Solvent activity may be regarded as a Critical Quality Attribute (CQA) of topical products. Evaporation of solvents from a topical formulation applied on the skin can lead to metamorphosis of the dosage form that can modulate active pharmaceutical ingredient (API) solubility and thermodynamic activity, and thereby, may impact drug delivery, bioavailability at the site of action, and therapeutic performance. The progressive change in excipient concentrations due to evaporation can result in a continually changing thermodynamic activity coefficient, until all the volatile components have evaporated. At that point, the majority of soluble drug that was available for delivery may be (super)saturated or may have precipitated in the residual formulation that delivers less drug to the skin thereafter. Traditionally, weighing the sample under controlled temperature and humidity conditions has provided an estimate of the dynamic processes of solvent evaporation. In this work, we have evaluated the solvent evaporation rate by measuring the weight loss gravimetrically and, in parallel, used mathematical simulations to predict the weight loss for similar experimental conditions.

OBJECTIVE

The aim of this study was to develop a mechanistic model to predict the likely evaporative loss under in-use conditions.

METHODS

Propylene glycol : water binary mixtures were prepared at various ratios as depicted in Table 1. Loss of volatiles (including water) were measured from formulation variants (Table 1) at 25ºC and 32ºC. A Franz cell donor chamber was used as the donor to hold the sample on a glass slide. A 250 µL volume of the formulation was added to the donor chamber and weight loss was measured for 6 hrs. Sampling was carried out every 10 minutes for the first hour, every 20 minutes from 1 h-2 h and hourly at 3 h, 4 h, 5 h and 6 h. A separate study was conducted to confirm the temperature of a known volume of the formulation using a Forward Looking Infra Red (FLIR) camera. Weight loss measurements were made in triplicate. A model was developed using MATLAB to predict the evaporative loss of volatiles (including water) under experimental conditions, using the Fick's law of diffusion. Initially Raoult's law was used to calculate the activity, and hence, the partial pressure of water vapored in equilibrium with the binary mixture. The evaporative water loss was modelled as steady state.

METHODS

Table 1: Formulation variants containing propylene glycol and water at different concentrations.

Components	F1	F2 (-5%)	F3 (-10%)	F4 (-15%)	F5 (-20%)	F6 (+ 5%)	F7 (+10%)	F8 (+15%)	F9 (+20%)	F10 (+60%)	F11(+100%)	F12(-60%)	F13(-80%)
Propylene glycol (PG)	25.00	23.75	22.50	21.25	20.00	26.25	27.50	28.75	30.00	40.00	50.00	10.00	5.00
Water	75.00	76.25	77.50	78.75	80.00	73.75	72.50	71.25	70.00	60.00	50.00	90.00	95.00

RESULTS

Based on the empirical results, the lowest loss of volatiles (including water) was observed for binary mixtures containing the lowest water content in the propylene glycol: water mixtures. Figure 1 compares the simulations with experimental values for 4 representative mixtures at 25ºC and 32ºC. A good correlation was observed between the experimental and predicted results with the model used. The experiment setup and temperature fluctuations (32.2 – 34.1˚C) are demonstrated in Figure 2. These were carried out to confirm that the temperature and humidity functions used in the model reflected the actual experimental conditions. In the event of larger fluctuations, these functions can be modified to generate a more representative fitting from the model.

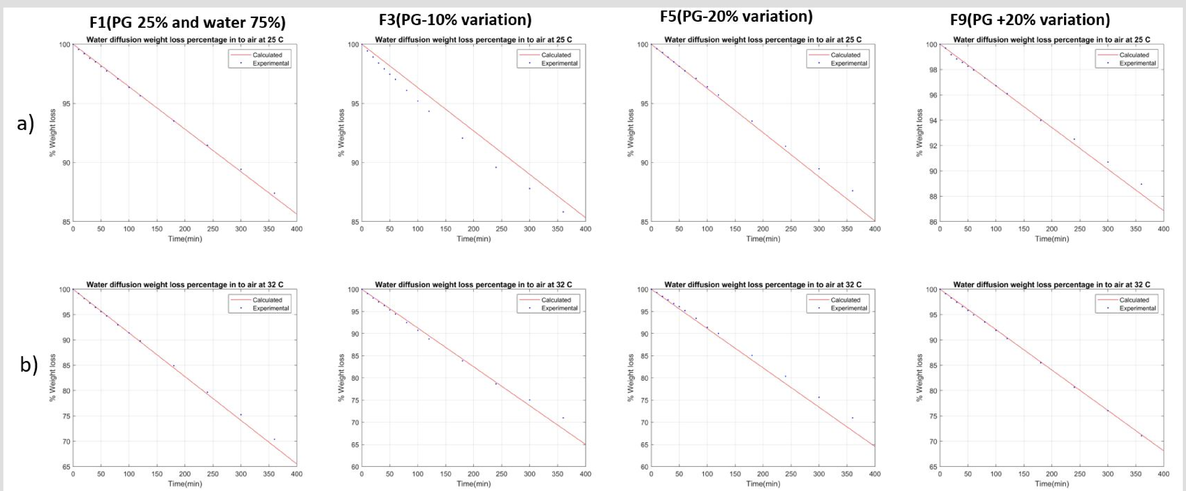

Figure 1- Representative graphs showing the evaporative water loss from water and propylene glycol binary systems (F1, F3, F5 and F9) at (a) 25ºC and (b) 32ºC. Measured experimental data (points) modelled through MATLAB model (lines). F1 is the reference binary mixture. F3 has a 10% reduction in PG. F5 has a 20% reduction in PG. F9 has a 20% increase in PG.

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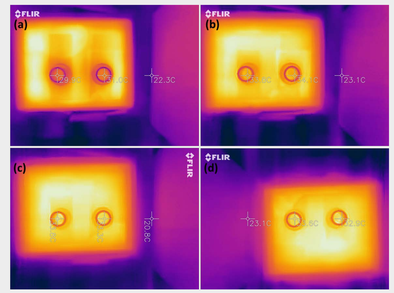

Figure 2- Thermal images of a known amount of formulation following application to a glass slide at time (a) 0, (b) 10 mins, (c) 25 mins and (d) 1 hour.

CONCLUSIONS

The combined use of Fick's law of diffusion with Raoult's law supported the development of a model with a good overall ability to predict these binary formulations' weight loss over time. Using these simulations minimizes the number of experiments needed to evaluate the solvent evaporation rate of a binary mixture at different ratios. These results suggest that, with further development and validation/ verification, such models have the potential to be a powerful and convenient tool to understand, simulate and predict dynamic processes, and their effect on related product performance attributes.

FUNDING/GRANT/ENCORE/REFERENCE OR OTHER USE

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