Investigating the Effect of Excipients on Solid State Degradation of Gabapentin
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Purpose
To understand the role of excipient properties on solid state degradation of gabapentin in the absence of any processing conditions.

Methods
Gabapentin was physically mixed (n=3) with different excipients namely tribasic calcium phosphate (Tritab®), dibasic calcium phosphate dihydrate (Ditab®) and anhydrous grade (Atab®), monobasic calcium phosphate and talc in 1:1 proportion. The mixtures were stored under controlled conditions of temperature and humidity (5 % RH and 50 °C) and analyzed for the concentration of gabapentin and lactam using reversed-phase, isocratic HPLC method. The lactam content (% mole) was measured at different time points for 696 h. An existing kinetic model proposed for the solid state degradation of gabapentin was used to analyze the collected data. Optimized model parameters were determined using nonlinear regression.

Results
The rate of lactam formation was observed to be greater in the excipient mixtures relative to gabapentin alone. The value of $G_0$ (compromised gabapentin) was constrained to be greater than 3 % mole for all mixtures based on the degradation profile of Tritab® with the highest initial lactam content. The rate constant $k_2$ (h⁻¹), responsible for spontaneous dehydration of compromised gabapentin, was seen to increase significantly in the presence of Tritab®, Atab®, Talc and Ditab®. The value of $k_2$ ranged from 0.0015 h⁻¹ for Tritab® to 6.89×10⁻⁵ h⁻¹ for monobasic calcium phosphate relative to 7.22×10⁻⁶ h⁻¹ in the case of gabapentin itself. In the case of Atab®, an inverse relationship between $k_2$ and excipient particle size was also observed. The rate constant associated with formation of compromised gabapentin ($k_1=0.00014$ mol⁻¹h⁻¹) did not change considerably in mixtures with monobasic calcium phosphate, talc and Ditab®, but decreased ($k_1=1.4×10^{-6}$ mol⁻¹h⁻¹) in the presence of Tritab® and Atab®.

Conclusion
Excipients impacted degradation of gabapentin in the absence of stressful processing conditions. The study indicated a catalytic effect of excipients, especially weakly basic agents on the transformation of gabapentin to lactam. Furthermore, based on the present data, the amount of compromised gabapentin in the unprocessed powder appears to be much higher than previous analysis suggested.