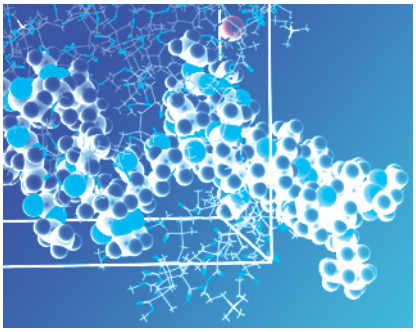
CASE STUDY

VALIDATION OF POLYMER-PLASTICIZER MODEL SYSTEMS FOR CONTROLLED DRUG RELEASE



Mechanical and physical properties of polymer and plasticizer mixes are key to the deisgn of controlled release systems.

Industry sector

- Pharmaceutical

Organizations

- University of Tuebingen
- University of Vienna

Products

- Materials Visualizer
- Discover,
- Amorphous Cell,
- COMPASS

When developing a new drug, the delivery and release systems to be used are of equal importance to the formulation of the active pharmacological ingredient (API). Such systems must be able to maintain an API payload in a stable condition for distribution, take the API to the internal location for release within a patient and release a controlled amount of the API over a predictable timeframe to be considered safe and effective.

Solid controlled drug release systems are commonly tablets or pellets coated with polymer films to control the release kinetics. The weak mechanical strength of the films can lead to handling difficulties during production and administration. More precisely, the possible rupture of the polymer film can lead to a dose dumping instead of the controlled release of the API. It is possible to improve safety by forming a matrix of diffusion controlling polymer (containing plasticizers) to embed the crystalline API. In both cases, the glass transition temperature (T_g) of the polymer system is of great importance in determining the stability of the drug formulation, its mechanical properties and the drug release profile.

In previous in silico models of drug release profiles, only pure polymer melts have been modelled. However, the majority of solutions in current use as 'real drugs' use mixed polymer-plasticizer systems. If an in silico modeling tool could be developed and validated that was accurate enough to model a mixed-melt delivery and release system, this would be of major significance in the pharmacological world.

Researchers at the University of Tuebingen and the University of Vienna[1] recently used atomistic molecular dynamic simulations to investigate how changing the ratio of plasticizer to polymer in a system affected the T_g and thus the release profile. The *in silico* modeling of the system was then validated against

experimental results in order to determine how accurate the computational methodology proved. The polymer used for this research was a cationic polymethacrylate (Eugragit® RS) and the plasticizer was triethylcitrate (TEC).

For the experimental values, samples of polymer (including varying amounts of TEC) were analyzed for T_g using a differential scanning calorimeter. The simulated values of T_g for the same melts were calculated using the polymer modeling tools in Materials Studio.

To determine T_g for each plasticizer proportion (^{W}TEC), 10 cubic simulation boxes were constructed using Amorphous Cell[2] (box length was approx. 3.5 nm), then minimised. The simulation box with the lowest energy configuration for each TEC proportion was then subjected to a molecular dynamics simulation, using the COMPASS[3,4], forcefield, at a temperature about 100 K above the supposed T_g, in order to obtain relaxed start structures with the correct density. The resulting model is then 'cooled' in 10 K steps to below T_g. Measurements of the computed specific volume of each mixture were taken, plotted against temperature and the T_g calculated from the kink in the graph showing the change from a glassy to a rubbery polymer[5].

In simulation, it was found that the percentage of plasticizer content within the melt had a direct and linear effect on the T_g of the melt, with T_g decreasing as plasticizer content increased. Although there were some discrepancies between computed and experimental results in some values of T_g, the trend was clearly visible in the simulated results, and validated by experimental results. This result means that in silico investigation and description of the physical and mechanical properties of release systems have now been made feasible by the application of atomistic molecular dynamic modeling techniques.

The ability to model such systems can only improve as the length and time scales of atomistic interactions improve, leading to the development of a valuable tool for studying properties such as the controlled release of drugs from a polymer matrix and opening the way to significantly reduce time to market for novel pharmaceutical formulations.

To learn more about Materials Studio by Accelrys, go to **accelrys.com/materials-studio**

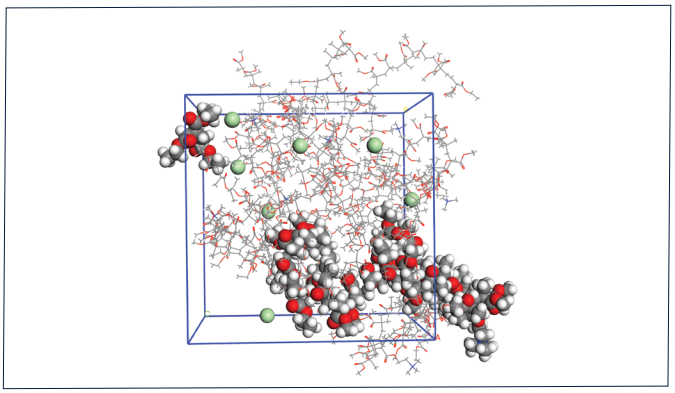


Fig. 1: *Simulation box (3.4 x 3.4 x 3.4 nm) with periodic boundaries showing 8 Eudragit® RS polymer chains and 2 TEC plasticizer molecules after a relaxation time of 2 ns at 460 K. One polymer chain and one TEC molecule are visualized in ball and stick style to demonstrate the size of the box in relation to the coiled polymer chain.*

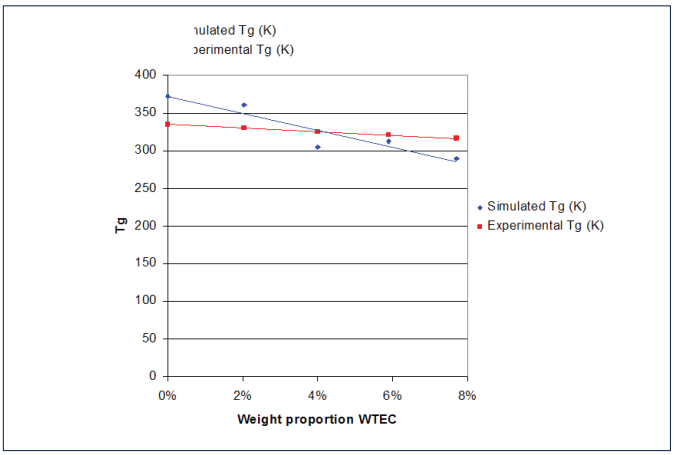


Fig. 2: *Variation of T_g with the weight content of plasticizers.*

REFERENCES

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