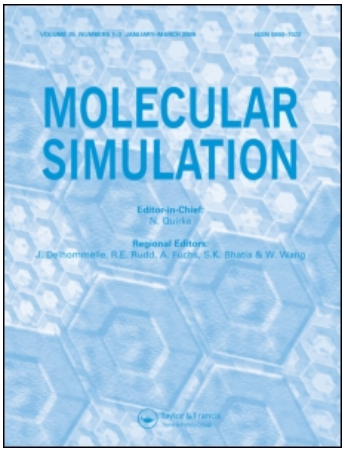

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Empirical molecular modelling of suspension stabilisation with Polysorbate 80

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Empirical molecular modelling of suspension stabilisation with Polysorbate 80

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Molecular modelling has been used successfully to predict the stabilisation of crystalline nanosuspensions of model pharmaceutical drugs by the surfactant Polysorbate 80. The ratio of the binding energy of the Polysorbate 80 to the binding energy of the drug to the surface of the crystal was found to correlate with the stabilisation of the nanosuspension.

Keywords: molecular modelling; Polysorbate 80; pharmaceutical; suspension

1. Introduction

The formulation of poorly water-soluble drugs into crystalline nanosuspensions is an area of active pharmaceutical research [1,2]. As the particle size is reduced, the surface area of the drug is increased, leading to greater bioavailability [3]. However, the stabilisation of crystalline nanosuspensions is non-trivial, especially given the limited number of surfactants that are also pharmaceutically acceptable excipients. Regardless, we have identified several surfactant combinations that can stabilise a variety of crystalline nanosuspensions. However, each new drug compound needs to be screened empirically with the various surfactant combinations to find the most stable formulation. This is time consuming, and can require a prohibitive amount of drug in early development phases [4]. This work was undertaken to develop a molecular modelling approach to rapid surfactant screening, which could identify stabilising surfactant systems for a particular drug, based on its crystal structure.

In this paper, we present the results of screening five model pharmaceutical drug crystals with the surfactant, Polysorbate 80. The model drugs were selected to offer a range of degree of stabilisation with Polysorbate 80, and also had crystal structures available in the Cambridge structural database (CSD).

2. Methods

2.1 Experimental

Crystalline nanosuspensions of the model drugs, nabumetone, carbamazepine (polymorph III), celecoxib, fluorometholone and compound A, an internal drug candidate, were prepared by high-pressure piston gap homogenisation (Avestin, Emulsiflex C5). With the exception of fluorometholone, each suspension was prepared by dispersing 1% (w/v) of crystalline drug in an aqueous surfactant solution containing 0.25% (w/v) of the surfactant Polysorbate 80, 0.5% (w/v) of the polymer Poloxamer 188 and 2.25% (w/v) glycerine for tonicity adjustment. The fluorometholone suspension was prepared with 0.25% (w/v) of the drug, 0.025% (w/v) Polysorbate 80, 0.05% Poloxamer 188 and 0.2% (w/v) glycerine. The coarse suspension was homogenised at a pressure of 20 kpsi until the target particle size of approximately 1 μm was reached. The particle size distribution was measured by static light scattering with a Horiba LA-920 particle size analyzer. Suspensions were also examined by light microscopy to ensure the suspensions were well dispersed. Aliquots of each suspension were stress tested to rapidly assess the physical stability of the formulation. The stress tests included centrifugation, a freeze–thaw cycle, three days of temperature cycling between 5 and 40°C and three days of shaking. The stability of some of the more promising suspensions was also determined in real time at several temperatures.

2.2 Molecular modelling

All molecular modelling was performed in Materials Studio®, version 4.2 (Accelrys, San Diego, CA, USA).

2.2.1 Crystal model

The growth morphology for each drug was calculated using the Morphology module of Materials Studio, using the Forcite energy method [5]. The COMPASS [6] force field was used for nabumetone, carbamazepine and fluorometholone. CVFF [7] was used for celecoxib and

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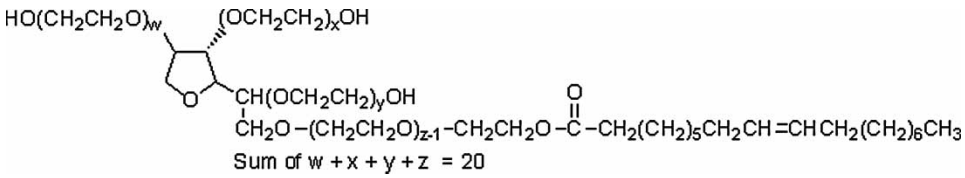

Figure 1. Structure of Polysorbate 80.

tamozolomide, because they contained atoms not defined in the COMPASS. COMPASS and CVFF were used because they can be used in Morphology, Forcite and Discover modules in Materials Studio. The crystal structures were obtained from the CSD [8], and the structure minimised with cell optimisation prior to the morphology calculation. The optimised cells were compared with their experimental structures to ensure that none had changed significantly, and thus that the force field used was appropriate.

For each drug, at least one crystal face was selected for modelling. To select a face for modelling, the morphology of the crystal was calculated employing the attachment energy method [9]. The faces with significant facet area and the highest attachment energy were selected first. These are the faces most likely to grow if the crystals ripen. A relatively flat face was also desirable for modelling. To prepare a face for modelling, the face was recleaved to give at least two layers of the crystal surface. Next, the surface was expanded by symmetry to give enough surface area to model the interaction with Polysorbate 80, at least 60 Å × 60 Å. Finally, a vacuum slab was prepared with at least 50 Å of space over the crystal face. See Figures 2 and 3 for an example of docking of both Polysorbate 80 and fluorometholone on the (0 2 0) face of fluorometholone.

2.2.2 *Surfactant model*

Polysorbate 80 is a mixture of compounds with the general structure shown in Figure 1. The structure has three arms consisting of chains of hydrophilic oxyethylene, and a fourth arm that terminates with a hydrophobic oleate tail. For modelling purposes, a single molecule of Polysorbate 80 with equal length arms was used (w, x, y and $z = 5$). The molecule of Polysorbate 80 was minimised, using the same energy parameters as the drug crystal. A molecule of each drug was also minimised, using the same energy parameters.

2.2.3 *Adsorption model*

The adsorption of both Polysorbate 80 and a molecule of the drug were modelled on each face. The Cartesian

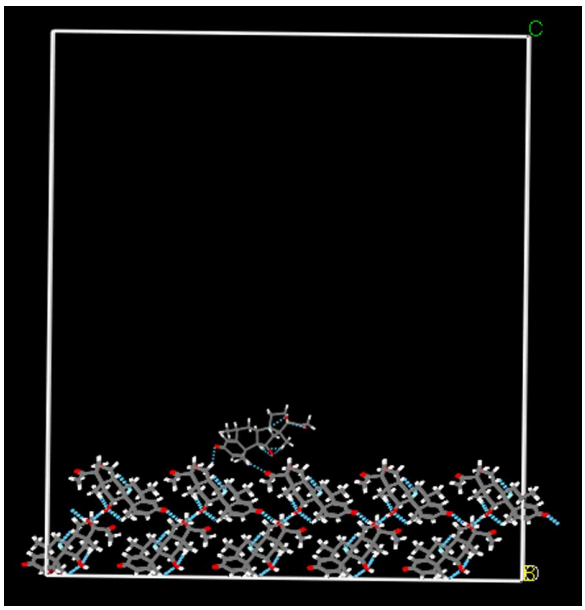

Figure 2. A fluorometholone molecule with the (0 2 0) face of fluorometholone.

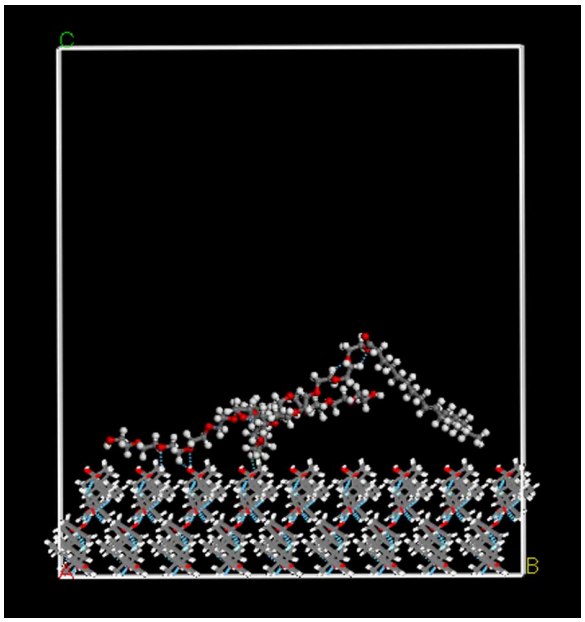

Figure 3. Polysorbate 80 with the (0 2 0) face of fluorometholone.

Table 1. Particle size stability of model drugs.

	Particle size (μm)									
	Initial		Temperature cycling		Shaking		Freeze–thaw		Centrifugation	
Drug	Mean	99%ile	Mean	99%ile	Mean	99%ile	Mean	99%ile	Mean	99%ile
Nabumetone	0.98	2.15	1.23	2.94	1.12	2.67	1.06	2.50	1.08	2.59
Fluorometholone	0.58	1.10	0.53	0.98	0.52	0.96	4.51	13.04	0.56	1.34
Celecoxib	1.24	2.97	2.01	6.28	1.74	5.27	1.41	3.84	1.73	5.97
Carbamazepine	1.32	4.65	1.56	6.21	2.41	12.32	1.35	4.45	1.42	4.50

position of each atom of the crystal was fixed for the simulation. A molecule of either Polysorbate 80 or the drug was positioned over the crystal face in a position where the additive molecule could interact with the surface. Hydrogen bonding was monitored to aid in the initial positioning of the additive. Next, a short molecular dynamics simulation was performed using the Discover module, usually a minimum of 500 steps, with at least 10 frames of output for each run. For each simulation, various starting conditions were used in order to find the lowest energy configuration. Forcite was used to calculate the energies of the total system, the additive alone and the crystal alone from the frame with the lowest energy.

This model of adsorption is greatly simplified, and provides only a rapid screening tool to aid in the design of empirical formulation studies. While the effects of the aqueous environment are critical to the adsorption of non-polar surfactants, they are ignored in this model. The simulations used only one molecule of one isomer of Polysorbate 80, and did not take into account various possible conformations of the oxyethylene side chains on the surface of the drug crystals. While these simulations do not give a complete picture of the adsorption of Polysorbate 80 on the crystal surfaces, they do give a prediction of the relative stability of the suspension in a matter of hours, using a Windows-based desktop computer.

3. Results

3.1 Experimental results

The model drugs represented a range of stabilisation with the Polysorbate 80/Poloxamer 188 surfactant combination. Crystal nanosuspensions of carbamazepine and compound A were the least stable with Polysorbate 80. Due to the aggregation of the initial suspension, and a limited amount of drug material available, the suspension of compound A was not subjected to further stability testing. The particle size results after stress testing for the other drugs are shown in Table 1. Celecoxib nanosuspensions stabilised with Polysorbate 80 were moderately stable. The Polysorbate 80-stabilised nanosuspension of fluorometholone was stable under most stress conditions. The stability of nabumetone nanosuspensions was the most enhanced by the Polysorbate 80 surfactant. The particle size of this formulation of nabumetone nanosuspension was stable for three months at −20 and 5°C. After six months of storage, ripening was observed microscopically by the presence of large needle-shaped crystals. It is important to note that we have found nabumetone to be a worst-case model drug for stabilisation of nanosuspensions. The reported surfactant system is the only one that we have found to stabilise nabumetone nanosuspensions for any significant length of time.

While this paper focused solely on the interactions of the Polysorbate 80 with the model drug compounds, it is important to note that Poloxamer 188 is also a surface active polymer present in each of the model suspensions. As a control, the model suspensions were also prepared with the Poloxamer 188 alone. The control suspensions prepared without Polysorbate 80 had significant aggregation in the initial suspensions, which worsened upon stress testing (data not shown). Future work will focus on the interactions between Polysorbate 80 and Poloxamer 188.

3.2 Molecular modelling results

The binding energy of each drug with its additives was calculated as follows:

$$E_{\text{binding}} = E_{\text{total}} - (E_{\text{crystal}} + E_{\text{additive}}),$$

where E_{total} is the energy of the system with the additive adsorbed, E_{crystal} is the energy of the crystal surface alone, and E_{additive} is the energy of the molecule of Polysorbate 80 or drug alone. The binding energies of each drug crystal and its additives are shown in Table 2. A more negative binding energy corresponds to a more favourable interaction. More importantly, the ratio of the Polysorbate 80 binding energy to that of the drug correlated well with the rank order stabilisation of the crystalline suspension. These stabilisation ratios are also presented in Table 2. A ratio of approximately 3 correlated to moderate stability; a ratio larger than 3, such as 9.40 for the nabumetone, correlated to excellent stabilisation. For carbamazepine and compound A, the drugs with poor stabilisation

Table 2. Molecular modelling $E_{binding}$ results.

Drug	Crystal face	$E_{binding}$ with Polysorbate 80 (kJ/mol)	$E_{binding}$ with drug molecule (kJ/mol)	Ratio of $E_{binding}$ Polysorbate 80/drug
Nabumetone	0 1 1	−414.47	−44.10	9.40
Nabumetone	1 1 0	−109.19	−52.55	2.08
Fluorometholone	0 2 0	−185.14	−40.88	4.53
Celecoxib	0 0 1	−122.51	−32.43	3.78
Celecoxib	1 0 −1	−235.68	−183.97	1.28
Compound A	1 1 −1	−141.84	−73.60	1.93
Compound A	1 0 −2	−85.44	−99.50	0.86
Carbamazepine	1 1 0	−33.89	−39.71	0.85

by Polysorbate 80, the ratio was near 1. In fact, for these systems, it took several simulations to obtain a negative binding energy result for both the Polysorbate 80 and the drug.

The face of the crystal used for simulations had a significant impact on the results. For example, nabumetone's fastest growing face (0 1 1) had the highest $E_{binding}$ with the surfactant. The slowest growing face (1 1 0) had much lower $E_{binding}$ with Polysorbate 80, but comparable $E_{binding}$ with the drug. However, the fastest growing face is the one that needs the most stabilisation to give a stable suspension. For celecoxib, the (0 0 1) face was the fastest growing, and showed a stabilisation ratio of 3.78 with Polysorbate 80. However, this face only represented 1% of the surface area of the calculated crystal morphology. The next fastest growing face (1 0 − 1) was 7% of the surface area, and only had a stabilisation ratio of 1.28. In the empirical study, the addition of Polysorbate 80 did greatly reduce the aggregation of the celecoxib suspension compared with the control suspension with Poloxamer 188 alone, but it did not completely inhibit the particle growth.

The faces with the greatest interaction with the surfactant were the ones with the most polar groups on the surface that could hydrogen bond with the oxyethylene arms of the Polysorbate 80 molecule. Figure 3 shows Polysorbate 80 with the (0 2 0) face of fluorometholone. This surface has both alcohol and amide groups easily accessible for hydrogen bonding with the oxyethylene groups. For comparison, Figure 4 shows Polysorbate 80 with the (1 1 0) face of carbamazepine. The surface of this face consists of hydrocarbons, and cannot hydrogen bond with the surfactant.

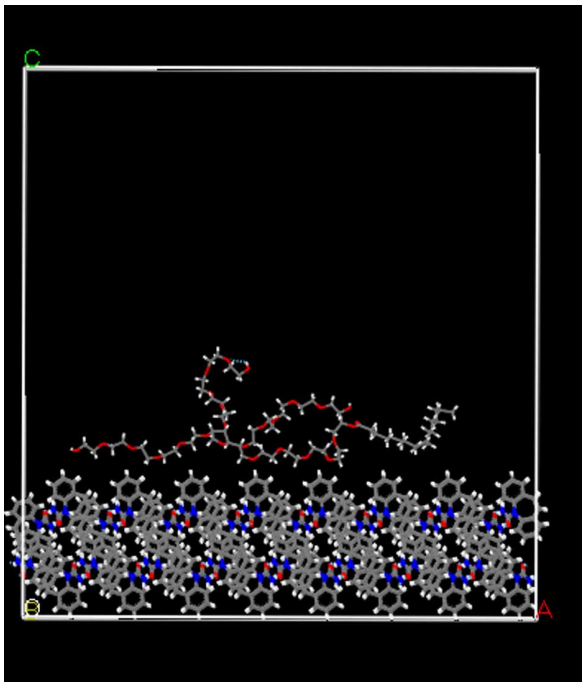

Figure 4. Polysorbate 80 with the non-polar (1 1 0) face of carbamazepine.

4. Summary and conclusion

In summary, we have used molecular modelling to predict the stabilisation of crystalline nanosuspensions by the surfactant, Polysorbate 80. The binding energy of surfactant and drug molecules with the crystal surfaces were calculated using Materials Studio. The ratio of the binding energy of surfactant to that of the drug gives a stabilisation ratio that correlates well with the stabilisation of the drug suspension.

The use of this technique for preliminary formulation screening could be beneficial because the molecular modelling experiments are less time consuming, and do not use valuable and limited drug material. The technique could be expanded for use with different surfactant compounds. This could help to prioritise the formulations screened by actual laboratory experiments, so that only the most promising surfactant systems would need to be screened to find a stable formulation.

Note

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References

[1] B. Rabinow, *Nanosuspensions in drug delivery*, Nat. Rev. Drug Discov. 3 (2004), pp. 785–796.

[2] T. Shah, D. Patel, J. Hirani, and A.F. Amin, *Nanosuspensions as a drug delivery system: A comprehensive review*, Drug Deliv. Technol. 7 (2007), pp. 42, 44, 46, 48–50, 52–53.

[3] F. Keisisoglou, S. Panmai, and Y. Wu, *Application of nanoparticles in oral delivery of immediate release formulations*, Curr. Nanosci. 3 (2007), pp. 183–190.

[4] S. Branchu, P.G. Rogueda, A.P. Plumb, and W.G. Cook, *A decision-support tool for the formulation of orally active, poorly soluble compounds*, Eur. J. Pharm. Sci. 32 (2007), pp. 128–139.

[5] A.K. Rappe, C.J. Casewit, K.S. Colwell, W.A. Goddard, and W.M. Skiff, *UFF, a full periodic table force field for molecular mechanics and molecular dynamics simulations*, J. Am. Chem. Soc. 114 (1992), pp. 10024–10035.

[6] H. Sun, *COMPASS: An* ab initio *force-field optimized for condensed-phase applications – Overview with details on alkane and benzene compounds*, J. Phys. Chem. B 102 (1998), pp. 7338–7364.

[7] P. Dauber-Osguthorpe, V.A. Roberts, D.J. Osguthorpe, J. Wolff, M. Genest, and A.T. Hagler, *Structure and energetics of ligand binding to proteins:* Escherichia coli *dihydrofolate reductase–trimethoprim, a drug-receptor system*, Proteins 4 (1988), pp. 31–47.

[8] F.H. Allen, *The Cambridge structural database: A quarter of a million crystal structures and rising*, Acta Cryst. B 58 (2002), pp. 380–388.

[9] A.S. Myerson, *Molecular Modeling Applications in Crystallization*, Cambridge University Press, New York, 1999.