# Problem set 2020-1

1. (10)

Estimate the molar solubility of betamethasone using its melting point and Log P. Obtain experimental values for the drug’s melting point from drugbank.ca or PubChem. A literature value for water solubility of betamethasone is approximately 0.60 mM. How does your predicted value compare to the experimental value reported in the literature. **Log10(Sw) = 0.8-0.01(Tm(deg C)-T)-logP**

Sw = 0.6166 mM

1. (10)

You are leading the drug delivery effort for a company working on new microtubule inhibitors. These drug candidates are not taxanes; they are a new structural class of inhibitors. The compounds were discovered and isolated form a marine source. It turns out that these marine compounds have significant toxicities as well as having extremely good microtubule inhibition activity.

There are three lead compounds that have been synthesized, in very small quantities, all have good activity. All of the analogs are very difficult to synthesize, and the company has limited resources, so a single lead compound will be chosen to take forward. These three leads have very different physical chemical properties and all are very difficult to solubilize in water and, even, in some organic solvents.

Estimate the water solubility at 25oC for the three lead compounds. The goal is to achieve 1 mM solubility. Do any of the compounds appear to reach this goal? Pick one analog for further study based on its water solubility.

Table 1.2. Properties of lead drug candidates.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Compound** | **MW**  **(Daltons)** | **Log P** | **TM**  **(oC)** | **SW**  **(mM)** |
| A36 | 633 | 1.5 | 343 | 0.1318 |
| A48 | 593 | 2.2 | 205 | 0.6310 |
| A67 | 621 | 5.6 | 195 | 0.0003 |

1. (20)

The project team has selected a compound to take forward to preclinical testing, based on its microtubule activity, solubility and feasibility of synthesis. You now lead the effort to solubilize the drug for use in preclinical and clinical studies. There is a strong desire to use the same formulation in both animal and clinical studies. The **target concentration is 10 mg/mL**, while using an aqueous based **non-ionic surfactant system**. By the way, the lead compound was named Pacific1 by the business development director, a Stanford graduate.

You have screened a number of surfactant systems to solubilize Pacific1 and found a newer grade poloxamer (P2020) that gives you the best solubility profile. The experimental data for the aqueous solubility of Pacific1 as a function of surfactant concentration is shown below in Table 1.3. Compare the **observed water solubility** below the critical micelle concentration (CMC) to the **prediction** you made in Question 2. Estimate an **approximate CMC** for the new poloxamer at 25oC and at 37oC. Select the **concentration of surfactant** to manufacture the sterile drug product for IV administration of Pacific1, at **>10/mg/mL**. In one paragraph give the **rationale** for the surfactant concentration you have selected. Are you confident that the drug will not **precipitate** upon infusion? Solubility increases at higher temperature of body.

Table 1.3. Solubility of Paxcific1 in aqueous solutions with P2020 surfactant

|  |  |  |
| --- | --- | --- |
| **Surfactant concentration (mg/mL) (Pacific1)** | **Solubility at 25oC**  **(mg/mL)** | **Solubility at 37oC**  **(mg/mL)** |
| 0 | 0.31 | 0.52 |
| 5 | 0.34 | 0.53 |
| 10 | 0.33 | 0.55 |
| 25 | 2.4 | 4.6 |
| 50 | 7.4 | 10.3 |
| 75 | 12.8 | 15.6 |
| 100 | 18.4 | - |

Plot solubility vs. surfactant conc. 🡪 point where solubility begins to increase linearly is CMC at each T.

1. (20)

A Phase 1 clinical study was done in an “all comers” cancer patient population to determine the pharmacokinetic properties and dose limiting toxicity of Pacifiic1. The maximum tolerated **single dose was determined to be 10 mg by IV bolus**. The dose limiting toxicity was peripheral neuropathy which was expected from the results of the preclinical animal studies.

There were a couple of remarkable observations from the Phase 1 trial. The first was the pharmacokinetic profile of the drug, which is shown in the Table 1.4 below. The drug appears to have a **very short half-life** in patients. Determine the **volume of distribution, the elimination half-life and the elimination rate constant** for the mean PK results for the IV bolus at 10 mg, (n=six patients).

The second surprising observation was a potential efficacy signal of the drug in pancreatic cancer patients. While there were only two pancreatic cancer patients in this phase I study, both patients showed some improvement within weeks of the first dose and were kept on study. They continued to be treated at 10 mg IV bolus every week thereafter. These two pancreatic patients both now have stable disease, but with some evidence of peripheral neuropathy.

Table 1.4. Mean pharmacokinetic profile for Pacific1 at a 10 mg bolus dose in cancer patients.

|  |  |
| --- | --- |
| **Time** | **Cp (ug/mL)** |
| 0 | Na |
| 1 | .088 |
| 2 | 0.075 |
| 3 | 0.061 |
| 4 | 0.051 |
| 6 | 0.034 |
| 8 | 0.026 |
| 12 | 0.0115 |
| 16 | Below quantification |

Plot and fit to either 1- or 2-compartment model; parameters are V and ke

1. (20)

From mouse tumor studies, it was established that **efficacy** was dependent on dose intensity (**average exposure over time**) and not maximum plasma concentration. However, the clinical and pharmacology teams both suspect that the chemotherapy-induced **peripheral neuropathy** (CIPN) is caused by the **maximum concentrations** observed during bolus dosing at 10 mg. The teams ask you to predict maximum plasma concentrations for the 10 mg dose administered as **zero order infusions** given over 1, 2,3,4,6,8 or 12 hours compared to the bolus administration. **Plot Cmax as a function of infusion time for each of these 10 mg administrations.**

Based on your PK analysis, the clinical team designed a clinical study with six treatment arms, shown in Table 1.5, to test the hypothesis that zero order infusion would reduce chemotherapy-induced peripheral neuropathy. Each treatment arm was tested in 8 chemotherapy-naive (with no prior chemotherapy) pancreatic cancer patients, to be dosed weekly for six weeks. The patients were evaluated for peripheral neuropathy at the end of week six, using a modified Total Neuropathy Score (mTNS). The scoring for the patients is summarized in Table 1.5, for each dosing paradigm.

Table 1.5 Modified Total Neuropathy Scores (mTNS) for patients treated for six weeks with 10 mg of Pacific1 in a Phase I/II clinical study.

|  |  |  |  |
| --- | --- | --- | --- |
| **Type of delivery** | **Cmax, ug/mL** | **mTNS at start of study (sd)** | **mTNS at six weeks**  **(sd)** |
| Bolus | 0.107 | 2 (1) | 13 (4) |
| 1-hour infusion | 0.097 | 2 (1) | 13 (3) |
| 2-hour infusion | 0.089 | 3 (2) | 12 (3) |
| 3-hour infusion | 0.082 | 1 (1) | 11 (3) |
| 4-hour infusion | 0.076 | 2 (2) | 9 (2) |
| 6-hour infusion | 0.065 | 2 (1) | 7 (2) |

Estimate the **baseline value (E0) value in the Emax model**, using the scores taken at the start of study. Plot the **six-week mTNS scores as a function of predicted plasma Cmax** for the patients. **Estimate the E max and EC50** parameters from the plot by visual inspection. The response curve is steep, so try a **SLOPE FACTOR (n) in the range of 4 to 6**. **Compare your Emax model predictions to the observed scores** for patients. Looking at your response curves, **does it appear likely that providing a lower Cmax compared to the six-hour infusion would further reduce peripheral neuropathy**?

1. (20)

Phase III clinical trials are going to be initiated in pancreatic cancer patients using the **six-hour infusion protocol at the 10 mg total dose**. The 10 mg six-hour infusion dosing paradigm will be taken all the way through registration and commercialization. However, there is a need for a follow-on drug delivery system that improves tolerability with a shorter infusion duration.

The company and project team are asking you to develop a **passively targeted nanoparticle that provides controlled release of Pacific1, with a duration of first order release over 12 to 24 hours, at a 10 mg dose**. This nanoparticle product would be developed in parallel to the aqueous infusion product but would require additional clinical testing and is anticipated to receive regulatory approval approximately two years after the commercial launch of the aqueous infusion product. It is expected that this drug delivery product would **reduce the peripheral neuropathy seen with the aqueous infusion product, shorten delivery time, and facilitate expansion into new indications.**

Using an emulsion process, you produce lots **PLGA, PLGA-PEG and Pacific1 nanoparticles with varying compositions**. The purpose of the design was to arrive at a composition for the nanoparticle that would produce a **12-to-24 hour release profile with a simple bolus administration**. The team wants to evaluate a single drug product candidate (nanoparticle formulation) in preclinical and clinical studies as soon as possible.

You have **already selected a specific MW and type of PLGA** for the experiments; it was very difficult to find a PLGA that would solubilize Pacific1 and incorporate it into the nanoparticle. You had **PEG 5000 covalently added to the selected PLGA to form a PEG-PLGA polymer**. The parameters you are **optimizing are the mole ratio of PLGA-PEG to PLGA and the drug load of Pacific 1 (weight fraction) in the nanoparticle**. The pharmacokinetic studies were done in male Sprague Dawley rats (n=8 per group), with an **average weight of ½ kg** and **plasma volume of 30 mL**. The experimental design is outlined in Table 1.6. You wanted the analytical group to develop an assay that could differentiate released Pacific1 from encapsulated, but there was not enough time. The PK assay will only give you **total Pacific1** and you will have to evaluate the curves carefully.

The mean results for the six different pharmacokinetic experiments are shown in the figures provided with the attachments.

Table 1.6 Experimental design for evaluation of drug load and polymer composition. Pharmacokinetics done in male Sprague Dawley rats (n=8 for each group), dosed at 1 mg/kg Pacific1 by IV bolus. Group names of each combination shown below.

|  |  |  |  |
| --- | --- | --- | --- |
| **PLGA-PEG ratio** | **0.05 Pacific1 (w/w)** | **0.10 Pacific1 (w/w)** | **0.20 Pacific1 (w/w)** |
| 0.10 | A5 | A10 | A20 |
| 0.20 | B5 | B10 | B20 |

For controlled release over long periods of time, need long circulation time – add PEG shields on surface of NP. Increasing relative concentration of PEG moves from “mushroom” model to “brush border” model, the latter of which is more successful at avoiding processing by the MPS system. Initial distribution phase is evidence of burst – excess drug that was not encapsulated in particles (exceeds solubility limit in PLGA and causes precipitation), inhomogeneity due to presence of drug in PLGA, etc. B5 is answer.