Problem Set # 3 DD 2020

Problem 3.1 (30)

Your goal is to develop a twice a day oral tablet with a relatively constant release profile and maintain plasma levels above the minimum inhibitory level for the treatment of a novel viral infection. The antiviral is very potent and has broad activity against different viral strains of an RNA virus. Unfortunately the half-life of the antiviral (named massvirone) has been determined to be 1.2 hours. This antiviral has demonstrated impressive efficacy in early clinical studies for patients who take the immediate release tablet 6 times a day at 10 mg per dose. Since it is expected that the new antiretroviral will be used in millions of patients, there is a significant need to develop a twice a day extended release oral product at 30 mg per tablet. The anti-viral massvirone has the following properties.

|  |  |
| --- | --- |
| **Property** | **Value** |
| Dose | 60 mg a day |
| Oral bioavailability (from a solution) | 93% |
| Elimination half life | 1.2 hours |
| Volume of distribution in patients  (one compartment) | 37 Liters |
| Colonic absorption | Unknown |
| Molecular Weight | 438 Daltons |
| Melting point | 294 oC |
| Water solubility | 0.44 mg/mL |
| Log P | 1.1 |
| pKa | No ionizable groups |
| Particle size | 25 um |
| Permeability | Rapidly absorbed in the small intestine |

It is suggested that you develop three different prototype extended release matrix tablet candidates. They will be based on 1) hydrophobic polymer release, 2) hydrophilic polymer matrix erosion and 3) an osmotic push/pull system. You have selected ethyl cellulose for the hydrophobic polymer matrix, HPMC as the erosion matrix polymer and polyethylene oxide for the osmotic system.

The Trade name of the polymer selected for ethylcellulose is EHTOCELTM, and you will use hot melt extrusion to produce the matrix tablets.

-**Draw the polymeric structure of ethylcellulose and explain why this is an appropriate choice for the hydrophobic matrix and describe the mechanism of release in your own words.**

The Trade name of the polymers selected for the osmotic erosion tablet is MethocelTM, and you will use wet granulation technology to produce the matrix tablets.

**Draw the polymeric structure of HPMC and explain why this is an appropriate choice for the hydrophilic matrix and describe the mechanism of release in your own words.**

The Trade name of the polymer selected for the Osmotic system is POLYOXTM, and you will use wet granulation and coating technology to produce the bilayer matrix tablets.

**-Draw the polymeric structure of PEO and explain why these polymers are appropriate choices for the Osmotic system and describe the mechanism of release in your own words.**

3.2 (30)

After optimization of each drug delivery system, you make tablet lots (500 tablet scale) of each of the polymer drug delivery systems. The hydrophobic polymer utilized hot melt extrusion, the hydrophilic polymer and the osmotic pump systems were optimized to be produced at this small scale using wet granulation and coating. Each formulation of tablets are evaluated by *in vitro* release experiments (n=6). The *in vitro* release experiments are performed in pH 6.0 phosphate buffer at 37oC and the mean values are shown in Table 3.2, where the immediate release tablet is run as a control. The statistical analysis indicates that the standard deviation for the extended release results are low, about 3% release, at each time point..

Table 3.2. in vitro release of extended and immediate release massvirone, pH 6.0 phosphate buffer at 37oC.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Hour | Immediate Release  10mg | ETHOCEL  1 x 30 mg | METHOCEL  1 x 30 mg | Osmotic pump  1 x 30 mg |
| 1 | 75 | 42 | 13 | 4 |
| 2 | 98 | 56 | 25 | 12 |
| 3 | 99 | 70 | 31 | 19 |
| 4 | 103 | 82 | 42 | 26 |
| 6 | - | 101 | 58 | 39 |
| 8 | - | 99 | 70 | 52 |
| 10 | - | - | 85 | 62 |
| 12 | - | - | 101 | 77 |
| 16 | - | - | 100 | 101 |

-**Use the power law to fit *in vitro* release curves and determine the diffusional exponent. Estimate the duration of release for each of the extended release prototypes. The power law should only be used up to 90% release.**

**-Are the power law exponents consistent with the expected mechanism of release for each polymer system?**

Problem 3.3 (40)

The pharmacology results and progress on the delivery systems are encouraging enough to proceed to Phase 1 human studies with the prototypes your team has developed. An open label single dose pharmacokinetic study using four different groups; 1) immediate release at 10 mg, 2) ETHOCEL at 30 mg, 3)METHOCEL at 30 mg and 4) Osmotic pump at 30 mg was initiated. The single dose pharmacokinetic study was done with healthy volunteers who were fasted overnight. Each of the formulations was taken with 8oz of water, plasma levels were determined as shown in Table 3.3.

Table 3.3. Plasma levels (ng/mL) in healthy volunteers following a single dose oral administration of different delivery systems of massvirone.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Hour | Immediate Release  10mg | ETHOCEL  1 x 30 mg | METHOCEL  1 x 30 mg | Osmotic pump  1 x 30 mg |
| 1 | 144 | 230 | 82 | 38 |
| 2 | 118 | 231 | 108 | 60 |
| 3 | 75 | 209 | 116 | 72 |
| 4 | 44 | 184 | 118 | 79 |
| 6 | 14 | 144 | 113 | 85 |
| 8 | 5 | 45 | 107 | 87 |
| 10 | 1 | 14 | 101 | 87 |
| 12 | 0 | 5 | 55 | 49 |
| 16 | 0 | 1 | 4 | 4 |
| 24 | 0 | 0 | 0 | 0 |

The criteria that the research group set for taking an extended release forward are:

1. The relative exposure to the Extended Release tablet (ER) compared to the Immediate Release (IR) is not less than 90%,

(AUC per mg ER/AUC per mg IR>0.90).

1. The maximum concentration observed for a single 30 mg ER dose should not exceed that of the 10 mg IR tablet
2. The time above 40 ng/mL (10 fold higher than the *in vitro* inhibitory concentration) should be greater than 10 hours.

**-Which of the ER formulations meet these criteria. Provide analysis to support your decision.**