Poorly water soluble drugs

Describe, with examples, TWO carriers that has been used to produce solid dispersions.

- **Polyethylene glycol (PEG)** melts stabilizes metastable forms due to increased viscosity of solid. It may also increase solubility by rearranging water structure or weak complexation. For example, griseofulvin.

- **Polyvinylpyrollidine (PVP)** has a melt……..

Targeted Drug Deliery

What are the main advantages of a targeted drug delivery strategy?

- To increase specificity and to reduce toxicity

What are the major features/components of Brentuximab vedotin (Adcetris) and what does each component contribute to the utility of this therapeutic?

- The three components are a drug, a linker in this case a dipeptide cleavable by cathepsin and an antibody, which is highly expressed on T cells. The drug is the active/cytotoxic, the linker cleaves in the environment of the tumour since cathepsin is overexpressed at the site of the tumour and the antibody targets specifically to lymphoma since it is an antibody to a proteins on the surface of T cells

Give two examples of materials that can be grafted to the surface of nanoparticles to produce a 'stealth effect'

- Polyethylene glycol (PEG) and sphingomyelin

List one example of passive targeting other than Caelyx. Include the challenges and approach in your answer.

Example: Docetaxel (Starpharma)

Challenges:

- Docetaxel rapidly cleared after IV administration and has little tumour affinity
- It also produces significant side effects after IV administration
- It is poorly water soluble, thereby requiring incorporation of surfactants in some of the formulations; however, surfactants may promote hypersensitivity issues – patient often put on corticosteroid and antihistamine beforehand

Approach: Use PEGylated docetaxel dendrimer

- It is highly soluble in absence of surfactant, hence no hypersensitivity issue
- Potential EPR into tumours
- Able to give at higher dose at one time as less free drug in general accumulation, hence reducing side effects

Compare between the passive targeting and active targeting strategies. Support your answer using relevant examples for each strategy.

Passive targeting involves the use of a carrier that has a passive affinity for a specific site (e.g. 'leaky' vasculature & 'compressed' lymph), which mainly relies on enhanced permeability and retention (EPR) effect. This increases specificity and decreases free drug concentration in general circulation and hence reducing toxicity. On the other hand, active targeting involves conjugation of a drug (or a carrier) to a targeting molecule (or group) (e.g. lectins & antibodies) that actively target to a specific site.

Passive targeting examples:

- Microspheres/nanoparticles
  - Has higher stability than liposomes
  - Materials used are albumin, gelatin, metal, biodegradable polymers
  - E,g, Abraxane

- Liposomes
  - Liposomal amphotericin B (AmBisome)
  - PEGylated liposomal doxorubicin (Caelyx)
  - Non-PEGylated liposomal doxorubicin (Myocet)

- Polymers
  - Linear polymer-drug conjugates
  - Dendritic polymer-drug conjugates

Active targeting examples:

- Receptor agonist / antagonist: usually at receptors with ……..

Ocular Drug Delivery

What are the three biopharmaceutical limitations to drug delivery to tissues deep within the eye?

i. Corneal permeability of lipophilic drugs
   - Cornea consists of 5 basic layers (epithelium, Bowman's layer, stroma, descemet's layer, and endothelium) and these barriers are designed to keep most things out.
   - Hence, drugs require specific set of properties to penetrate (i.e. moderate log P, unionized, and moderate aqueous solubility).

ii. Two competing routes of drug clearance in transcorneal absorption:
   - Nasolacrimal drainage/clearance to GI tract
     - Can be increased by irritation due to instillation of drugs (has 4 factors that cause irritation, namely surface tension, osmolarity, pH and particulate formulation) & therefore reduce residence time & transcorneal absorption
   - Absorption into conjunctiva (conjunctiva have large SA & very vascular)
   - Overall, only 5% of drug able to be absorbed into aqueous humour

iii. Low buffering capacity of tears (pH 6.9-7.5)
   - Instillation of solutions where pH is >>7 or <<7 may lead to irritation and increases tear throughput / nasolacrimal clearance & therefore reduce residence time & transcorneal absorption
   - Ionised drug more readily cleared in tears due to solubility and lack of absorption

Bioequivalence

Describe the role of the Therapeutic Goods Administration and its responsibilities in ensuring the safety, efficacy, and quality of medicines available in Australia.

- TGA administers Therapeutics Goods Act 1989
- TGA decides if products are suitable for listing or require registration
- TGA assesses new **over-the-counter products** for quality, efficacy and safety
- TGA re-assesses benefit-risk profile of existing products
- TGA regulates **complementary medicines**

(more to come)

Quality Assurance

- The good academic record would provide the applicant an additional advantage over other applicants with the similar background. However, whether or not to offer the applicant a chance of interview depends on other factors such as:
    - Previous working experience in the quality control department of an pharmaceutical company
        - A Quality Control Manager is responsible in releasing the batch of raw material for manufacturing and releasing the batch of final products
        - Therefore, the QC manager needs to be equipped with knowledge with the testing procedures and documentations before releasing the batch
    - Critical thinking, analyzing and judging skills
        - A QC manager requires competent judging skill to make the decision to release the batch after analyzing the test results
    - Leadership as QC manager is the leader of QC team
    - Qualifications have to be relevant to pharmaceutical science
- Given the important role of QC manager which require extensive technical knowledge, competent decision making and leadership skills that all need to be built up from years of working experience, it is unlikely for the applicant who has just graduated from Monash Uni one year ago to be offered a chance of interview

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- The feasibility of this proposal is depends on two factors
    - The cost associated with the manufacturing
    - The profit generated with the manufacturing
- The cost associated with the manufacturing is quite high because:
    - The manufacturing of steroid drugs require complete segregation from the current manufacturing plant as the impact of cross-contamination is serious, which impose an additional cost for premise and equipment

(more to come)