**Pharmaceutical Product Design**

100 Years Ullmann's: From Drug Discovery to Formulation Development, from Pilot Plant to Scale-Up

The final design of a pharmaceutical product is very lengthy and involves several stages. The beginning stage is the drug discovery phase. During this phase, the active pharmaceutical ingredient (API) is determined. Once the API is known, the formulation of the pharmaceutical product must be determined. Other chemical compounds, called excipients, are added to the formulation to help stabilize the API and increase its efficacy. Successive phases involve design of the manufacturing process, from pilot plant to scale-up. The final delivery method of the pharmaceutical product is determined, with oral methods such as tableting or encapsulation the most common choices. Finally, the product can be approved and marketed.

Product design principles can be applied to many of the stages in the pharmaceutical development process. In practice, many new pharmaceutical products are discovered and developed using exhaustive trial-and-error approaches. Rational product design aims to limit trial-and-error expenses through optimization and property estimation of the target molecule. Property prediction can identify excipients which would most improve the API's stability and efficacy. The final delivery of the drug in vivo can also be improved by designing molecules that have properties allowing the drug to be delivered at the desired conditions.

Several concepts are vital to product design for pharmaceuticals. From a process systems engineering (PSE) standpoint, the most important are the target product profile (TPP), design specifications, critical quality parameters, and health, safety and environmental (HS&E) considerations. The target product profile sets the design space for the pharmaceutical product, while the other considerations place constraints on the design space. For the final design of the pharmaceutical product to be successful, the design should match the target product profile as closely as possible.

**General Concepts in Pharmaceutical Product Design**
The concepts of TPP, design specification, critical quality parameters, and HS&E considerations hold for all aspects of pharmaceutical product design.

The TPP will determine which API and excipients are considered. The ultimate delivery method will also be influenced by the TPP. While designing any of the components of the pharmaceutical product, design specifications and quality parameters will constrain the possible targets considered. The specifications will also be used to identify the optimal molecule for the considered product component.

The TPP is established based upon a determined consumer health need. All key attributes of the product are listed in the TPP. The values for the key attributes are the ideal product properties. Some key attributes are the desired therapeutic effect, the efficacy, the dosage, and the safety or tolerability of the final pharmaceutical product. The key attributes are what defines the pharmaceutical product. The TPP should be met by the final design as close as possible.

The design specifications are a list of user-defined specifications that the final product must meet. Such specifications could include solubility, particle size, and pH (for liquid products). Quality parameters are added as well. Such parameters include cosmetic concerns such as the color and overall appearance of the pharmaceutical product. Taste is important in products that are delivered orally. Other quality parameters include desired shelf life and consistency of the product from batch to batch. Health assessment of the pharmaceutical product is very important. Toxicity must be evaluated during the product development process, for both the API and the final product. Often, established excipients are chosen for the formulation due to time constraints. Similarity to previously approved excipients is often cited as leading to similar toxicological effects, avoiding additional regulatory approval. Environmental concerns play a part, as use of environmentally benign excipients is encouraged. For example, much work has been done to determine alternates to the chlorofluorocarbons (CFCs) used in metered dose aerosols.

**API Design and Development**

The API is often designed with the goal of interacting with a certain biomolecule in the patient's cell. Usual target biological molecules are enzymes and receptors on the cell's surface. The API must also have minimal interactions with the biological molecules that are not being targeted. The stability and bioavailability of the drug molecule is also a concern when selecting a successful API. The constraints placed on the performance of a drug create a limited design space for the final selected molecule.
Drug candidates are identified by three primary routes:

1. The most traditional route is discovery by serendipity. Scientific observation has led the discovery of many drug compounds, such as the discovery of the antibacterial properties of penicillin.

2. Combinatorial chemistry can create hundreds of candidate molecules. High-throughput screening is used to scan molecular libraries and narrow down the candidates to several molecules that best match the desired properties.

3. Computational screening is an increasingly popular choice for drug development.

Newer methods have led to direct design of the API. Molecular screening allows for the three-dimensional structure of biological molecules to be modeled. Structure-based drug design uses the structural information of the target molecule to design an API that will favorably interact with the target. Optimization of the API molecule can lead to a drug that will perform at a high level. Structure-based drug design offers a method of direct design of a compound rather than experimental screening of a large number of molecules.

**Ligand Screening**

Combinatorial chemistry and high-throughput screening focus on generation of a large number of candidate drug compounds. Testing reduces the number of compounds immensely to a small number of lead compounds that are then used for further testing. There are considerable time and cost investments involved with experimentally screening a large number of molecular species. The desire for a more rational drug design and development process is clear, where both time and cost requirements are reduced and success rate of the final pharmaceutical product is increased. The application of computational methods is increasingly being used to improve the drug development process.

Once a biological target is identified, a drug molecule can be designed which will bind with the target. Often the design is concerned with small molecules, but peptides and polymers are also design candidates. Ligand binding is a process used to model the interactions between a drug and its biological target, which is referred to as a receptor. The part of the drug molecule that binds to the receptor is defined as a ligand. The primary constraint for the drug candidate is the ligand-receptor interaction. Two fundamental approaches are used in drug design:
1. Receptor-based approaches use knowledge of the three-dimensional structure of the biological target, usually a protein.

2. Ligand-based approaches use information about compounds that are known to bind to proteins to search for new molecules possessing biological activity.

**Receptor-Based Approaches.** Molecular simulation is used in receptor-based design to model the three-dimensional structure of a binding site on a target. Once identified, the binding site is categorized based upon hydrogen bonding, electrostatic, or hydrophobic interactions. The interaction sites can be used to limit the number of possible ligand structures that are considered. With the binding site finalized, a docking tool can then be used to computationally model ligand-receptor interactions. Two basic methods are employed in modeling ligand docking with the binding sites. (i) Lock and key approaches assume that the binding structure is rigid. Flexible ligand molecules are then docked with the fixed structure. (ii) Induced fit docking approaches allow for flexibility in both the ligand and the receptor structure and are therefore much more computationally intensive. To reduce computation costs, the protein backbone is often assumed to be rigid, while the side chains are allowed to be flexible. Docking algorithms use scoring functions, usually based on free-energy, to evaluate the interactions between drug candidates and identified docking sites. A docking that minimizes the scoring function being utilized identifies successful ligand candidates.

**Ligand-Based Approaches.** When the three-dimensional structure is not precisely known, ligand-based approaches can be successfully employed. A ligand-based strategy is based on the known structure or topology of one or more ligands. From this known ligand, a pharmacophore can be established. The pharmacophore acts as a pseudo-receptor, which can be used to screen for binding sites that are structurally similar on a biological target. Then ligand docking models can be used as seen in structure-based design. To develop the pharmacophore model, the set of known ligands must be evaluated using one of two common approaches. The first approach is to develop a target quantitative structure-activity relationship (QSAR) that must exist between the ligands and a pharmacophore. Other molecules can then be screened to determine how well they match the QSAR specifications. The second approach computes molecular descriptors and similarity indices for the ligand set. Other molecules can then be screened for a match to the similarity index for a specific pharmacophore. All molecules that match on a similarity index are considered fits for the pharmacophore that the index was developed for.

Various computational approaches can be used for receptor-based and ligand-based drug design. The approaches vary in the fundamental building blocks, the basic
algorithm employed, and the scoring function used. The computational approaches may only work for one approach or may apply to either design strategy. The fundamental building blocks are either atoms or commonly used fragments composed of several atoms. The main algorithms used in receptor-ligand approaches are: depth first search, breadth first search, random, Monte Carlo/simulated annealing, and evolutionary algorithms. The scoring functions are diverse. Some of the most common include force field, empirical scoring, and pharmacophore constraints. All scoring approaches are an attempt to approximate binding energies.

**Structure-Based Drug Design**

Once key binding fragments, or ligands, have been identified through computational screening, further lead optimization can be used to generate the final drug molecule. The ligand alone may not successfully match the specified TPP of the pharmaceutical product. Of specific concern is the absorption, distribution, metabolic and excretion properties (referred to as the ADME properties).

The ligand identified through receptor-ligand design serves as a scaffold to which functional groups can be added to improve the properties of the drug molecule that will become the active pharmaceutical ingredient. A growing procedure can be used to add fragments to the docked scaffold. Fragments can be selected from a database of molecular segments that are often found in drug-like molecules. When scanning molecular libraries, traditional QSAR methods are often used. New adaptive functional group reordering techniques use random sampling of the molecular fragments to measure targeted properties. Estimation over the entire library can then result in discovery of fragments or molecules with desirable property values. When multiple functional groups can be added to the ligand scaffold, the number of combinations can be very large. Using iterative rounds of adaptive functional group reordering, an optimal drug molecule can be more quickly found than when QSAR methods are used.

**Pharmaceutical Formulation Design**
Once a drug molecule has been selected, a formulation for the final pharmaceutical product must be selected. The physical and chemical characteristics affect the choices available during the formulation design. Pharmaceutical research and development has been primarily concerned with the design and development of the API, with formulation design as a secondary concern. Contemporarily, the pharmaceutical industry has experienced diminished productivity and fewer drug approvals. A possible reason for this trend is that the criteria for drug design are not sufficient.

API design often focuses on the potency and selectivity of the chosen drug molecule, as represented by ligand-receptor binding. However, other criteria are important for success of a pharmaceutical product. The final product must have an acceptable safety profile, as indicated by the TPP. The drug must have the correct pharmacokinetic profile as is often represented by the ADME properties. Finally, the drug must lend itself to successful scale-up and production. The correct formulation can improve the API's performance and ensure that the final pharmaceutical product meets all criteria. By considering formulation concerns throughout the drug discovery and development process, the final product will have more likely match the desired TPP and have an increased chance of regulatory and commercial success. Traditionally, the selections of excipient molecules for the formulation have been made from a preapproved list. The rationale is that using excipients that are generally regarded as safe (GRAS) or have been included in previous FDA approved submissions reduces regulatory concerns and therefore overall time to market. Similarity to previously approved excipients is often cited as leading to similar toxicological effects, avoiding additional regulatory approval. However, new progress made in biologics and the development of novel drug delivery systems has led to increased importance of innovation in formulation design.

By looking at new combinations of excipients or design of new excipients, formulation design can contribute significantly to the success of a pharmaceutical product. Computational molecular design is a possible strategy for the development of novel excipients. Optimization of molecular structure has been shown to create novel molecules with improved properties in many fields such as solvents and polymers.

**Formulation Properties and Selection**

The selection and design of an API focuses on optimizing the therapeutic or biological effect of the pharmaceutical product. However, for the product to be successful, the formulation must contain excipients that will lend the right physical
properties to the final product. Such physical properties include solubility, density, viscosity, and particle size. The combination of known excipients can be optimized to best match the target physical properties.

The desired physical properties can be used to place restrictions on the types of excipients used and the amount used in the formulation. Experimental design can use the valid ranges of excipient amounts to rationally determine what excipient mixtures should be tested. The experiments on excipient mixtures then determine the properties of each mixture. The mixture that most closely matches the desired target properties can be identified and used in the final pharmaceutical product. Visualization techniques can be used to easily compare the experimental results. The excipient mixture that best matches the target can be identified visually very quickly and the pharmaceutical product development can proceed.

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