#### 3.5.6.2 Excipient Compatibility

Whereas the choice of excipients starts with the stages of formulation, some excipients are historically used in specific drug formulations; for example, if the newly discovered drug is a cephalosporin for use as an intravenous product, compatibility with arginine or sodium carbonate would be advised, as these are the most commonly used active excipients used for solubilization. Similarly, for drugs that are likely to be compressed, compatibility with common ingredients of compression and disintegration are the plausible choices at this stage. The relative emphasis on excipient interaction would depend on how the company research is planned; in many situations, the preformulation group is more closely aligned with the drug discovery group, and many of these studies are left to the formulation group.

## 3.6 Transport Across Biological Membranes

### 3.6.1 Drug Efflux and Multidrug-Resistance Studies

The problem of MDR has gained increasing importance in recent years, particularly in the fields of tumor therapy and treatment of bacterial and fungal infections. One of the major mechanisms responsible for the development of MDR is the overexpression of drug efflux pumps. These membrane-bound, ATP-driven transport proteins efflux a wide variety of natural product toxins and chemotherapeutic drugs out of the cells and give rise to decreased intracellular accumulation of these compounds. Thus, inhibition of efflux pumps is a versatile approach for overcoming MDR, and several compounds are in clinical phase III studies. The main target is Pgp, which is responsible for MDR in tumor cells, and transport systems in *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*. Owing to the fact that three-dimensional (3D) structures of the proteins at atomic resolution were not available, drug development was performed solely on the basis of ligand design. However, electron microscopy studies, as well as X-ray structures, of three bacterial efflux pumps may open the door to target-based drug design in the near future.

The lipophilicity of drug molecules (represented as the logarithm of the *n*-octanol/water partition coefficient) often strongly correlates with their pharmacological and toxic activities. It is therefore not surprising that there is considerable interest in developing mathematical models capable of accurately predicting their value for new drug candidates. The key importance of lipophilicity in biostudies is discussed for $\beta$-blockers. Examples of their lipophilicity-dependent pharmacological properties, including pharmacokinetic, pharmacodynamic, and clinical aspects, are reviewed. Comprehensive lipophilicity compilations of $\beta$-blockers are not available so far. Log *P* calculations with 10 programs for 30 clinically relevant $\beta$-blockers are presented for the first time in this review.

Modulators and inhibitors of multidrug efflux transporters, such as Pgp, are used to reduce or inhibit MDR, which leads to a failure of the chemotherapy of, for example, cancers, epilepsy, bacterial, parasitic, and fungal diseases. Binding and transport of first-, second-, and third-generation modulators and inhibitors of Pgp take into account the properties of the drug (H-bonding potential, dimensions, and $pK_a$ values) and of the membrane.