promising drug molecules started becoming available in quick succession and formulation scientists were faced with the tasks of rapid formulation. It was realized that if, keeping in mind the subsequent needs, a few physicochemical properties of the new drug are investigated prior to the formulation; an efficient, elegant formulation development is relatively easier. This was the period, probably, when concept of preformulation started evolving. It eventually has become part of official requirement of new drug approvals (NDAs).

Preformulation is the first learning phase or prior step of formulation development for a new drug molecule. It involves generating information regarding physicochemical properties of the drug, its interactions with the excipients, stability profile both in solid and solution state and preliminary *in vivo* properties. A detailed understanding of the properties of the drug substance is essential to minimize formulation problems in later stages of drug development, reduce drug development costs, and decrease the product's time to market (i.e., from drug substance to drug product). The motives of preformulation studies are to choose the correct form of the drug substance, evaluate its physical properties, and generate a thorough understanding of the material's stability under the conditions that will lead to development of an optimal drug delivery system. Information gathered during preformulation is of immense importance for the development of a stable dosage form. Preformulation study begins at the point after biological screening, when a decision is made for further development of compound in clinical trials (CT). The fact that the quantity of the drug available at this early stage is often very limited (normally in milligrams) makes the job of the preformulation scientist even tougher. Thus, it becomes important to decide the priorities and selectively determine only those preformulation parameters, which affect drug performance, and dosage form development, which are meaningful. Before beginning the formal preformulation programme the preformulation scientist must consider a few factors, which include:

1. The amount of drug available.
2. The physicochemical properties of the drug already known.
3. Therapeutic category and anticipated dose of the compound.
4. The development schedules.
5. The nature of information a formulator should have or would like to have.

Goals of preformulation study

1. To establish the necessary physicochemical parameters of a new drug substance.
2. To establish the compatibility with common excipients.
3. To determine the kinetic rate profile, and
4. To establish its physical characteristics

A typical preformulation design is given in Table 1.3 and briefly discussed below. After these considerations a preformulation scientist can take up the actual studies.

UV spectroscopy

The first requirement of any preformulation study is the development of a simple analytical method for quantitative estimation in subsequent steps. Most of drugs have aromatic rings and/or double bonds as a part of their structure and absorb light in UV range. UV spectroscopy, being a fairly accurate and simple method, is a preferred estimation technique at early preformulation stages. The absorption coefficient (equation 1) of the drug can be determined by formula

$$E_1' = \frac{AF}{X} \qquad \ldots(1)$$

where A = absorbance, F = dilution factor, and X = weight of drug (mg).

It is now possible to determine concentration of drug in any solution by measuring absorbance.

Table 1.6. Recommended solvents for preformulation screening

Solvent	Dielectric constant (e)	Solubility parameters (d)	Application
Water	80	4.4	All
Methanol			
0.1 M HCl (pH 1.10)	32	147	Extraction, separation, dissolution (gastric), extraction of base
0.1 M NaOH (pH 13.1)			Extraction of acid
Buffer (pH 6–7)			Dissolution (intestinal)
Ethanol	24	12.7	Formulation
Propylene glycol	32	12.6	
Glycerol	43	16.5	
PEG 300 or 400	35		

soluble in water and in the partitioning solvent. If the compound has a log P = 5, then the compound is 100,000 times more soluble in the partitioning solvent. A log P = –2 means that the compound is 100 times more soluble in water, that is, it is quite hydrophilic.

Log P values have been studied in approximately 100 organic liquid-water systems. As it is virtually impossible to determine log P in a realistic biological medium, the octanol-water system has been widely adopted as a model of the lipid phase. While there has been much debate about the suitability of this system, it is the most widely used in pharmaceutical studies. Octanol and water are immiscible, but some water does dissolve in octanol in a hydrated state. This hydrated state contains 16 octanol aggregates, with the hydroxyl head groups surrounded by trapped aqueous solution. Lipophilic (unionized) species dissolve in the aliphatic regions. Generally, compounds with log P values between 1 and 3 show good absorption, whereas those with log Ps greater than 6 or less than 3 often have poor transport characteristics. Highly non-polar molecules have a preference to reside in the lipophilic regions of membranes, and highly polar compounds show poor bioavailability because of their inability to penetrate membrane barriers. Thus, there is a parabolic relationship between log P and transport, that is, candidate drugs that exhibit a balance between these two properties will probably show the best oral bioavailability.

Many solvents have been used as organic phase in determination of partition coefficient (e.g. hexane, CCl_4, $CHCl_3$, C_6H_6, diethyl ether etc.) but the largest data is available with n-octanol. Although, partition coefficient alone cannot provide an understanding of *in vivo* absorption, yet it can give a fair idea of hydrophilic/lipophilic nature of drug. This may be useful in anticipating the drug absorption.

Dissolution

Newly discovered lead compounds that are ultimately formulated into drug delivery systems should be capable of existing either in a molecular dispersion, such as solutions or in an aggregate state, such as tablets, capsules, suspensions, and so on, that are readily rendered into finer state of dispersion and dissolution. Regardless of the stage of aggregation in the final formulation, the active pharmaceutical ingredient (API) must be released from the drug delivery system and as the first step, should be dissolved in an aqueous environment; this will then be followed possibly by one or more transfers across non-aqueous barriers. To determine

efficient analytical technique. Accordingly it is a method of choice in stability indicating investigations.

Stability

Stability of a drug substance or product is defined as the extent to which a product or substance remains within specified limits of identity, strength, quality and purity throughout its intended period of storage and use. Knowledge of inherent stability of drug is important as it is utilized to decide excipients, processing parameters, storage conditions and to predict shelf-life. The objective of the stability study in pre-formulation design is to identify situations, which may pose threat to stability of active agent and help avoid or control them. This objective can be achieved by investigating stability at three fronts:

1. Solid state stability (of drug alone).
2. Compatibility studies (stability in presence of excipients).
3. Solution phase stability.

Solid state stability

The stability of drugs in solid dosage form is most important and common for the study of degradation of drug substance or drug product that are generally decomposed by either first- or zero-order profile. Chemical unstability normally results from either of the following reactions: hydrolysis (solvolysis), oxidation, photolysis and pyrolysis. Chemical structure of the drug is the determinant of susceptibility of drug to either of the above attacks. Esters and lactams, and to lesser extent, amides are prone to solvolysis. Unsaturation or electron rich centres in the structure make the molecule vulnerable for free radical mediated or photo-catalysed oxidation. Physical stability is influenced by physical properties of drug. Amorphous materials are less stable than their crystalline counterparts. Rate of degradation in a series of vitamin A esters was inversely related to their fusion temperature. Denser materials are more stable to ambient stress.

Thus, a thorough knowledge of drug's structure and physical properties is helpful in designing the stress conditions to challenge its suspected weakness in a stability programme. The data obtained under stress conditions can be utilized to predict the stability under normal storage conditions.

Elevated temperature studies

These studies are carried out by accelerating the rate of decomposition, preferably by increasing the temperature of reaction conditions. The elevated temperatures commonly used are 40, 50 and 60°C in conjunction with ambient humidity. The samples stored at highest temperature are observed weekly for physical and chemical changes and compared to an appropriate control (usually a sample stored at 50°C). If a substantial change is seen, samples stored at lower temperatures are examined. If no change is seen after 30 days at 60°C, the stability prognosis is excellent. Corroborative evidence must be obtained by monitoring the samples stored at lower temperatures for longer durations. Data obtained at higher temperatures can be extrapolated using Arrhenius treatment of storage temperatures (Figs. 1.19 and 1.20).

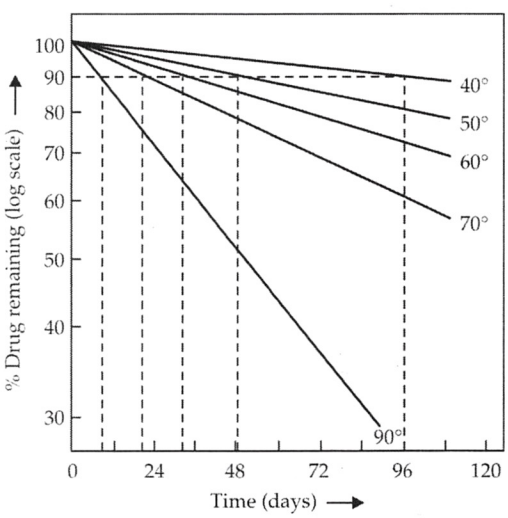

Fig. 1.19. Time in days required for drug potency to fall to 90% of original value.

constituent by extraction procedures that may include maceration or percolation.

- **Oromucosal preparations:** Oromucosal preparations are liquid preparations, containing one or more active substances intended for administration to the oral cavity and/or throat to obtain a local or systemic effect. Preparations intended for a local effect may be designed for application to a specific site within the oral cavity such as the gums (gingival preparations) or the throat (oropharyngeal preparations).

  Preparations intended for a systemic effect are designed to be absorbed primarily at one or more sites on the oral mucosa (e.g. sublingual preparations). For many oromucosal preparations, it is likely that some proportion of the active substance will be swallowed and may be absorbed via the GI tract. Oromucosal preparations may contain suitable antimicrobial preservatives and other excipients such as dispersing, suspending, thickening, emulsifying, buffering, wetting, solubilizing, stabilizing, flavoring and sweetening agents [British Pharmacopoeia, 2007]. Several categories of preparations for oromucosal use may be distinguished:

- **Gargles:** Gargles are aqueous solutions intended for gargling to obtain a local effect. They are *not to be swallowed*. They are supplied as ready-to-use solutions or concentrated solutions to be diluted. They may also be prepared from powders or tablets to be dissolved in water before use. Gargles may contain excipients to adjust the pH, which, as far as possible, is neutral.
- **Mouthwashes:** Mouthwashes are aqueous solutions intended for use in contact with the mucous membrane of the oral cavity, usually after dilution with water. They are *not to be swallowed*. They are supplied as ready-to-use solutions or concentrated solutions to be diluted. They may also be prepared from powders or tablets to be dissolved in water before use. Mouthwashes may contain excipients to adjust the pH to neutral, as far as possible.
- **Gingival solutions:** Gingival solutions are intended for administration to the gingivae by means of a suitable applicator.
- **Oromucosal solutions and suspensions:** These are liquid preparations intended for administration to the oral cavity by means of a suitable applicator.
- **Oromucosal drops, sprays and sublingual sprays:** These are solutions, emulsions or suspensions intended for local or systemic effect. They are applied by instillation or spraying into the oral cavity or onto a specific part of the oral cavity such as spraying under the tongue (sublingual spray) or into the throat (oropharyngeal spray). A list of commonly used oral liquid preparation is presented in Table 2.1.

REGULATORY CONSIDERATIONS

GMP consideration

Quality, efficacy and safety of a medicinal product have always been a matter of concern for public. GMP is advocated for maintenance of high quality standards in pharmaceutical manufacturing. Government of India included GMP under schedule M of Drug and Cosmetic Act vide G.S.R. 735(E) dated June 24th 1988. The schedule M has again been amended in a major way by the Drugs and Cosmetics (8th amendment) Rules, 2001 w.e.f. December 11th 2001 and embraces Rules 71, 74, 76 and 78 under the Drug and Cosmetics Rules, 1945. GMP includes requirements for factory premises, work space and storage area, health, clothing and sanitation of workers, medical services, sanitation in manufacturing premises, equipment, raw materials, master formula records, batch manufacturing records, manufacturing operations and controls, reprocessing and recovery, product containers and closures, labels and other printed materials, distribution records, records of complaints and adverse reactions, and