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View PDFVolume 29, Issue 9, September 2021. Pages 1029-1042 rights and content When a promising new chemical entity is synthesized, it needs transformation to appropriate formulation in order to show a better and desirable action at appropriate site. Preformulation study is a phase which is initiated once the new molecule is seeded. In a broader way, it deals with studies of physical, chemical, analytical, and pharmaceutical properties related to molecule and provides idea about suitable modification in molecule to show a better performance. Study of these parameters and suitable molecular modification can be linked to generation of effective, safer, stable, and reliable pharmaceutical formulation. Therefore, preformulation study is an approach for generation of pharmaceutical formulation which utilizes knowledge and area application of toxicology, biochemistry, medicinal chemistry, and analytical chemistry. The highlighted chapter is framed with a vision to provide an in-depth knowledge about pharmaceutical formulation development.preformulationphysicochemical propertiesprodrugstability studiesanalytical profilingDiscovery of a new drug entity is a huge milestone in science and it becomes even more important if it passes toxicity screening as the potential benefits outweigh the side effects. The ultimate effect of the new chemical entity depends on its availability at the site of action once it is administered through appropriate route in appropriate form. So for this reason, a new challenge is offered after successful pharmaceutical and toxicological screening that is to transform potential active new drug entity into a pharmaceutical formulation. It can be broadly elaborated as "a phase which works on study of physical, chemical, analytical, pharmacokinetic, and pharmacodynamic properties of new chemical entity and utilize the obtained results to design and develop an effective, stable, and a safer dosage form." Preformulation study is there for the multidisciplinary approach and utilizes involvement of several aspects of pharmacology, toxicology, clinical pharmacy, biochemistry, medicinal chemistry, and analytical chemistry (Figure 1). The preliminary objective of preformulation phase or study is to lay down foundation for transforming a new drug entity into a pharmaceutical formulation in such a way that it can be administered in a right way, in right amount, and on perhaps the most important at right target. The secondary objective preformulation study is to provide longer stability to the formulation by proper designing and protecting drug component from environmental condition and to evaluate performance of developed formulation.Outline of preformulation studies.AdvertisementFollowing the successful pharmacological screening of an active molecular entity, one has to be sure about the appropriate molecular form of active molecular entity. The optimization of molecule is needed with respect to stability of molecule under normal environmental condition or with respect to enhancing the performance of that molecule like bioavailability and stability. To imbult these virtues into a molecule, efforts are made to optimize a molecule into forms of salts, solvates, polymorphs, and more importantly prodrug.Nearly half of the drug molecules that are marketed as drug products are administered in salt form. Converting a molecule into a salt form is perhaps the most widely used approach to significantly enhance the performance of a molecule. This improvement can be made in area such as follows:Performance (increased solubility and bioavailability)Improved stability (hydrolytic and thermal stability)Better organoleptic properties (taste masking)Increased patient compliance (decreased side effects)Modified release dosage formsThere are several factors that are needed to be considered while selecting appropriate salt form. The main factor that determines the appropriate salt form is type of formulation that is to be developed.Mostly, sodium and hydrochloride are the most suitable forms to be used if formulation to be developed is tablet, oral solution, or injectable. With sodium and hydrochloride as salt form, there is always enhanced solubility and hence better bioavailability is assured. For example, the propionic acid derivative naproxen exists in free acid form and has lower water solubility and hence less bioavailability. When it is converted to sodium salt, its water solubility is increased by severalfold and hence better bioavailability is assured. Similarly, tolbutamide, an oral hypoglycemic agent has 1000-fold greater water solubility than corresponding free acidic form.Another factor that determines the type of salt form is type of formulation to be developed. For example, when the formulation to be developed is suspension, insoluble salt forms like tosylate, estylate, and embonate are the preferred salt forms.Therapeutic indication is another factor that affects the selection of salt form. For example, if drug is indicated in the treatment of hypertension, the use of sodium or potassium salt is avoided. This is the main reason behind development of potassium salt of diclofenac, which is preferred over sodium salt. Diclofenac potassium can be given as analgesic in patient with history or current occurrence of hypertension.As the regulatory perspective, selection of salt form must meet regulatory requirements and must be free from toxicity. For example, use of lithium salt is strictly prohibited.For immediate release formulations, generally sodium or hydrochloride salts are preferred as they show better solubility. For delayed release formulation, one can prefer low solubility salt form such as tosylate, estylate, and embonate.Increased patient compliance can be obtained by converting a molecule to a salt form. For instance, injection of cephalosporin generates the pain at site of application. However, when it is administered as morpholine salt, the pain at the site of application was reduced to many folds. In similar way, salt form can improve the taste adaptability by masking the taste and odor. Piperazine can be improved organoleptically by converting into salt with adipic acid [1].Prodrug is the chemically modified inactive derivative of active form with optimized properties and better in vivo performance. Almost one-tenth of the pharmaceutical products are used as prodrug with main aim of improving bioavailability by avoiding first-pass metabolism, improved drug absorption, and organ selective transport. So prodrug can be defined as inactive form that undergoes biotransformation and converted to active form to elicit its pharmacological effect. Development of prodrug depends on specific property of drug that needs improvement and mostly with respect to stability, improving bioavailability [2].In recent times, science has moved to "cod drugs," "hard drugs," and "soft drugs," where cod drug consists of two pharmacologically active components, which are complexed to form a single molecule (e.g., sulfasalazine, Levodopa-Entacapone). Soft drugs are the modified derivatives with predetermined metabolism, so that after exerting pharmacological action for suitable time, its metabolite can be eliminated from body. Main aim of developing soft drugs is to avoid toxicity associated with formed metabolites. Hard drugs are opposite to soft drugs, where the modifications are made in such a way that its original properties are retained but are not prone to chemical or biological transformation to avoid generation of metabolites or to increase the biological activity.Apart from abovementioned classification, there are two main broad classes of prodrug that are carrier-linked prodrug and bioprecursor prodrug. In carrier-linked prodrug, the drug is linked to a carrier moiety by a temporary covalent linkage. Cleavage of a carrier prodrug generates a molecular entity of increased bioactivity (drug) and at least one side product, the carrier, which may be biologically inert. Carrier molecule or functional group can be easily removed in vivo, usually by hydrolytic cleavage [3]. There are several criteria for being a carrier-linked prodrug, which are as follows:Link between drug and a carrier molecule must be a covalent linkage.Carrier-linked prodrug is inactive or less active than the parent compound.The linkage between the drug and the carrier molecule must be broken in vivo.The prodrug, as well as the in vivo released transport moiety, must be nontoxic. The generation of the active form must take place with rapid kinetics to ensure effective drug levels at the site of action and to minimize either alternative prodrug metabolism or gradual drug inactivation.Bioprecursor prodrug results from a molecular modification of the active principle. In vivo transformation of drug generates a new metabolite [4].Several goals of developing prodrug are as follows:Improving unfavorable physical properties:Improvement in water solubility.Improvement in lipophilicity.Improvement in chemical stability.Improvement in organoleptic characteristics.Improving pharmacokinetic properties.Improving bioavailability.Improving penetration power through membrane.Improved first-pass metabolism.Target-specific drug delivery.Classical example of target-specific drug delivery in selective metastatic colon cancer is capecitabine which is a prodrug of 5-fluorouracil. Capecitabine requires triple-phase transformation to be converted to its active form 5-fluorouracil. The first metabolism takes place in liver by action of enzyme carbonyl esterase. This transformed form then enters the tumor cells by selective uptake and is again transformed by deamination by action of enzyme cytidine deaminase. This form in tumor cell is converted to 5-fluorouracil by enzyme thymidine phosphorylase, which is only present in the tumor cells.The other example of target-specific delivery is release of sulfasalazine in colon by action of bacterial reductase where sulfasalazine is converted to sulfapyridine and 5-amino salicylic, where the later formed is the active molecule.One of the best ways to improve the lipophilicity is the esterification of the molecule. For example, terbuthaline is orally active beta-2 agonist and is indicated in bronchial asthma. It suffers significantly higher dose due to lower lipophilicity. Its prodrug bambuterol has improved lipophilicity as well as chemical stability and thus requires considerably lower dose than terbuthaline [5].AdvertisementDetermination of chemical properties indicates the absorption behavior as well as stability of a molecule in the body. One of the most widely determined chemical properties includes partition coefficient (Log P), dissociation constant (pKa or pKb), and stability of molecule under a variety of conditions. Each property has significant value in development of formulation.Partition coefficient (Log P) value is defined as ratio of unionized drug distributed between aqueous and organic phase. Oil-water partition coefficient gives the idea about drug's ability to cross the lipidic membrane. Lipophilic/hydrophilic balance is one of the most important contributing factors for optimum drug absorption and delivery. Due to lipidic nature of biological membrane, the amount of drug absorbed depends heavily on its lipophilicity. It is the unionized form of molecule that has better lipophilicity and hence it has received so much importance.LogP=CoilCwaterEquilibriumIf the value of Log P is 0, it indicated that drug has equal distribution in water and partition solvent. Value of Log P less than 1 is indicative of higher water solubility and value greater than 1 is indicative of higher lipid solubility. For optimum solubility and absorption, a proper hydrophilic-lipophilic balance is necessary.Determination of Log P value in biological system is next to impossible task, so several methods are available to determine partition coefficient of molecule in vitro, which are as follows:Shake flask methodChromatographic method (HPLC)Computation based on softwareCountercurrent/filter probe methodHighly used method is shake flask method that utilizes octanol-water system to determine drug's partitioning behaviors. There are several reasons behind selection of octanol as partitioning solvent, which can be explained as follows:Octanol is believed to mimic the lipidic character of biological membrane as it contains polar head and nonpolar tail.Octanol is organic compound that is immiscible with water; however, some of the water is expected to be present in polar head portion.Solubility parameter for most of the drugs resembles with that of octanol.Like partition coefficient, dissociation constant (pKa) is the property that determines the solubility in pH-dependent environment and extent of ionization. It is the extent of ionization that determines the absorption as only unionized form can be absorbed and hence it becomes essential to determine the pKa value of molecule. pKa value determination gives idea about site of absorption.Weakly acidic drugs having pKa value around 4 are best absorbed from stomach as they are predominantly present in unionized form. Basic drugs having pKa value of around 8 are best absorbed from intestine as they are predominantly present in unionized form. % ionization can be determined by the following equation:%Ionization=10pH-pKa+110pH-pKa+100E2Most of the strong acids and strong bases are present in ionized form throughout GIT and hence poorly absorbed. But it is also true that most of the pharmaceutical entities are derivatives of weak acids and weak bases and hence absorption is not an issue.One of the most silent chemical parameters that define the pharmacological activity is the type of isomer. Many molecular entities exist in racemic form, but only one form gives the desirable pharmacological activity. Other present isomer may be devoid of pharmacological activity or may exhibit deleterious side effects. Most of us are known to teratogenic tragedy of thalidomide. Thalidomide exists as racemic form. Racemates contain equal amount of enantiomer, which are known as either levorotatory (-) or dextrorotatory (+) based on its ability to rotate the plane of polarized light [6]. It was introduced as a sedative agent. The S-enantiomer of thalidomide was a teratogenic agent, while R-enantiomer was effective as a sedative agent. Lack of knowledge about chiral selectivity leads to disastrous consequence. In recent times, single enantiomer is dominating the market over the racemate form due to better pharmacological performance. Nowadays, racemic switching or chiral switching is used in which racemic mixtures are developed as single enantiomers. Several single enantiomers are preferred over racemic form (e.g., levofloxacin (ofloxacin), esomeprazole (omeprazole), escitalopram (citalopram), and desloratadine (loratadine)) [7].Overview of the same is given in Table 1. For better clinical performance of the molecule, it has become necessary to study the chirality of the molecule. In most of the cases, it can be studied by optical rotatory dispersion and circular dichroism [8].Drug in racemic formUse active enantiomerAdvantage offeredOfloxacinLevofloxacinS(-)-enantiomerEnhanced activity against pneumococciCetrizineLevocetirizineR(-)-enantiomerLess sedative action with same activityKetoprofenDexketoprofenS(+)-enantiomerReduction in dose of ketoprofen (half) with same effectiveness and lesser GT-related side effectsIbuprofenS(-)-enantiomerS(-)-ibuprofen is over 100-fold more potent inhibitor of cyclooxygenase. So three times dose reduction was achieved than racemic mixtureOmeprazoleEsomeprazoleES(+)-enantiomerEsomeprazole shows better bioavailability than R-enantiomer and maintains pH above 4 in patients with GERD with least variabilitySalbutamolLevalbuteroLRacemic form and S-enantiomer hyperresponsiveness in sensitized patients with loss of bronchodilator activity. (R)-salbutamol produces significantly greater bronchodilation than the equivalent dose of the racemateAdvantage of racemic switching.The main objective of determining stability of molecule is to identify the conditions in which molecule is susceptible to deteriorate and to determine degradation pathway. The mechanism of degradation and condition provides the idea about proper designing of formulation, suitable molecular modification, appropriate storage condition, and selection of proper packaging material.The major mechanisms by which a molecule undergoes degradation are hydrolysis, oxidation, photolysis, and racemization. Out of these mechanisms, hydrolysis is perhaps the most studied after oxidation.Hydrolysis involves reaction of a molecule with water resulting in cleavage of a chemical bond within the molecule. If readily hydrolyzable functional groups are available, then reaction proceeds even at faster rates, making the molecule ineffective. Molecules containing esters and amide functional groups are prone to hydrolysis and especially the ester derivatives, which may lead to formation of carboxylic acid or an alcohol.Effectiveness of molecule therefore depends on hydrolytic stability of molecule. For example, lidocaine is amide derivative of procaine, which is ester derivative used as local anesthetic. As ester derivative is more readily hydrolyzed; its duration of action is short while amide derivative is more stable and hence used as long-acting local anesthetic.Beta-lactam antibiotics are susceptible to hydrolysis and hence they are supplied as dry powder injection where they are reconstituted before intravenous administration.Many molecules can undergo oxidative degradation, which involves exposure of molecule to atmospheric oxygen or autoxidation by free radicals. However, in some cases, oxidation can be initiated in presence of light or elevated temperature. So degree of oxidation can be controlled by avoiding exposure to lights and storage at controlled temperatures. Even the extent of oxidation can be controlled by addition of antioxidants. The extent of oxidation for a given substance can be studied by passing oxygen through the solution of substance, or it can be achieved by addition of hydrogen peroxide to the solution of substance.Photolysis refers to decomposition of a molecule by absorption of energy when exposed to light. Exposure to light not only brings photodegradation but may trigger oxidation. It is absorption of shorter wavelength components that may bring oxidation than longer wavelength components. Prior knowledge of photochemical behavior can provide guidance regarding storage condition, packaging, and handling condition. In most of the cases, the photochemical behavior of molecule is studied in the range of different spectral regions that are 200-290, 290-320, 320-400, and 400-700 nm. For example, riboflavin and vitamin B12 are susceptible to photodegradation directly and oxidation induced by light. So to avoid the decomposition, the formulation containing vitamin B12 and riboflavin is stored in amber color vials. Amber color bottles do not allow the ultraviolet radiation to pass through, which is the main factor for photodegradation [9].It is an event where optically active molecule becomes inactive without any change in molecular composition. Such study is of highest importance when racemic mixture form is used. Racemization leads to either loss of pharmacological action or toxic effect may be enhanced by severalfold. Racemization is mostly affected by the conditions like pH, type of solvents, presence of light, and temperature. So main goal in this study is to design optimum condition in which molecule can remain stable [10].AdvertisementMost often than not, new chemical entity exists in solid form and the properties under study during preformulation phase are bulk property characterization and micromeritic property characterization. Bulk property characterization includes study of polymorphism, crystallinity, density, nature of molecule like deliquescence or hygroscopicity and micromeritic characterization includes study of particle size, shape, porosity, and density. As most of the new chemical entities are solids, they exist either as amorphous or in crystalline state. Either of the form imparts the two main virtues that are stability and solubility.One of the most widely studied techniques during preformulation analysis is solubility profile of drug candidate. It is the backbone study of preformulation stage that determines the performance of developed formulation. Solubility and permeability forms the scientific basis of biopharmaceutics classification system (BCS), which can provide framework for designing type of drug delivery system. Table 2 provides basic idea about basic BCS classification and link between solubility, permeability, and type of targeted formulation.BCS classSolubilityPermeabilityApproaches in formulation developmentClass 1High/LowConventional solid oral dosage formClass 2Low/HighUse techniques to improve surface area or improving solubility by addition of cosolvents or surfactantsClass 3High/LowUse of permeability enhancersClass 4Low/LowUse approaches of classes 2 and 3Correlation of solubility and permeability with BCS class and associated approach in formulation development.The solubility of a drug is the amount of the drug that dissolves in a given solvent to produce a saturated solution at constant temperature and pressure. Table 3 provides outline of different levels of solubility. For conversion of drug molecule into an effective oral formulation, it must have good aqueous solubility for better absorption. Solubility is not an independent parameter but it relies on several properties like crystal characteristics, temperature, pH, complexation, and molecular structure. There are several techniques, which are available to improve the solubility of drug candidate, which are as follows:Chemical modification of drugAddition of cosolvent or surfactantParticle size reductionHydro-tropyComplexationDescriptive termPart of solventVery solubleLess than 1Freely soluble1-10Soluble10-30Sparingly soluble30-100Slightly soluble100-1000Very slightly soluble1000-10,000Practically insoluble or insoluble10,000 or moreAmorphous drugs have randomly arranged molecules or atoms in the molecular lattice. Typical amorphous forms are obtained by techniques like precipitation, rapid cooling after melting, and lyophilization. One of the most important advantages associated with amorphous form is the higher solubility and hence the higher dissolution rate. More often than not drugs with low water solubility lead to poor bioavailability and variable clinical response. So, polymorphic form may overcome this problem with main challenge of stability. The associated disadvantage is the reduced stability in comparison to crystalline form, so upon storage, amorphous forms tend to revert to more stable form. But the risk-to-benefit ratio remains in the favor of amorphous form and hence is more preferred for product development. For example, novobiocin when administered in crystalline form showed no therapeutic activity, while amorphous form showed better absorption from gastrointestinal tract with significant therapeutic response [11].Crystalline form is characterized by regular spacing between molecular lattices in three-dimensional structure. One of the striking advantages associated with this form is the impeccable stability at a cost of lower water solubility than amorphous form. For example, Penicillin G as sodium or potassium salt in crystalline form has the better stability and hence stable and better therapeutic response in comparison to amorphous form. Various techniques are available to study crystallinity like X-ray, differential scanning microscopy, differential thermal analysis, hot stage microscopy, and the most important one that is scanning electron microscopy.Polymorphism is the ability of a compound to crystallize as more than one distinct chemically identical crystalline species with different internal lattices or crystal packing arrangement. Type of crystalline species generated depends on temperature, solvent, and time. Polymorphs are chemically same but mainly differ with respect to physical and pharmaceutical properties. As different types of polymorphs exhibit different types of solubility, stability, and therapeutic activity, it has become mandatory to have preliminary and exhaustive screening to identify all the polymorphic crystal forms for each drug. Similarly, chloramphenicol palmitate exists in three different polymorphic forms, namely, A, B, and C. Form B has higher solubility and better dissolution profile, while form A is more stable one but low serum concentration was observed. During formulating suspension of an antelmintic drug oxyzanolide, transformation of unstable polymorph to more stable leads to different crystal size and causes caking. In case of creams, crystal growth leads to gritty texture and in case of suppositories one can observe different melting behaviors and leads to formulation instability [12].When solvent molecules are incorporated into structure of drug molecule, it is known as solvate. When water is incorporated as solvent in the structure, they are termed as hydrates. Pseudopolymorphs are the different crystal form of solvates. This phenomenon is also referred to as solvohydrism. For example, during synthesis of ethinylestradiol, crystallization of final product is achieved by using solvents like acetonitrile, chloroform, methanol, and water. As a result, four different solvates are generated. Differentiation of pseudopolymorphs can be studied by hot stage microscopy (melting behavior). True polymorphs melt slightly and form a globule, while pseudopolymorphs give bubble in the system due to generation of vapor or gas from entrapped solvent.Two different types of polymorphs are well defined and are known as "monotropic polymorphs" and "enantiotropic polymorphs." Monotropic polymorph can be reversibly changed into another form by change in temperature and pressure and the latter involves one-time transition into another form. With respect to stability and solubility, again polymorphs can be classified as stable and metastable polymorphs. Stable polymorph is one of the most physically stable polymorphic forms and has highest melting point, lowest energy, and least aqueous solubility, while metastable polymorph refers to forms other than stable polymorph and has highest energy, low melting point, highest aqueous solubility, and hence shows better bioavailability. Metastable polymorphs have wider application in developing formulation but still only one-tenth of metastable forms are having practical use as they suffer from the stability issues [13].Hygroscopicity can be defined as the capacity of a compound to absorb atmospheric moisture. Amount of moisture absorbed depends on atmospheric conditions and surface area. Deliquescent substance absorbs moisture to a greater extent and liquefies itself. The main reason behind study of this property is because changes in the moisture level can influence chemical stability, flowability, and compressibility to a greater extent.In European pharmacopoeia, hygroscopicity is described by four different classes after being stored at 25°C at relative humidity of 80% for 24 hours.Slightly hygroscopic: After abovementioned storage condition, if overall increase in weight is greater or equal to 0.2% but less than 2% w/w.Hygroscopic: After abovementioned storage condition, if overall increase in weight is greater or equal to 0.2% but less than 15% w/w.Very hygroscopic: After abovementioned storage condition, if overall increase in weight is greater than 15% w/w.For this study, samples under analysis are exposed to range of controlled relative humidity prepared with saturated aqueous salt solutions (Table 4). One can link flowability and relative humidity by amount of moisture uptake (Table 5).Substance used% RH achievedSilica gel90%Potassium acetate20%Calcium chloride30%Potassium bromide85%Water100%Utilization of different salts to give environment with different RH.Process-affected propertiesPrecipitationSurface area, particle size, shapeEncapsulationParticle shape and sizeCrystallizationParticle shape, size, crystallinity/amorphous natureChemical reactionSurface area and particle shapeUse of different process to control particle size, shape, and surface area.Moisture level uptake can be monitored by techniques like thermogravimetric analysis (TGA), Karl Fischer titration, and gas chromatography.Particle size greatly affects a number of quality parameters like dissolution rate, solubility, bioavailability, content uniformity, and lack of grittiness. Application of particle size study during preformulation stage is described as follows:When solubility is major issue, one may significantly improve the solubility by reducing the particle size (increased surface area).In case of suspension, particle size is the most important parameter, which determines the stability and quality of formulation. Too much reduction in the particle size leads to generation of charged particle and hence unstable system. On other hand, larger particle size leads to caking.Due to nonuniform particle size distribution, there is significant risk associated with content uniformity in case of potent formulations.A number of methods are available to determine particle size, which are as follows:MicroscopySedimentation rateCoulter counter methodSurface area determination by nitrogen adsorption methodApart from particle size, particle shape plays an important role during preformulation phase as the shape of particle may influence surface area, flow properties, and compaction force. A drug particle may exist in different forms like spherical, angular, acicular, needle, oval, or rough. It is a well-accepted fact that a spherical particle has the maximum area and uniform flow property. The maximum surface area ensures the better solubility. For topical products that are working as abrasives, irregular particle shape is more preferred. Table 3 provides idea about various methods, which can control particle shape and size and provide better results needed to design a formulation.Density can be defined as ratio of mass of a substance to its volume, which greatly depends on particle size distribution and shape. The main problem arises during determination of bulk volume is the voids, which can be interparticulate, open, and closed intraparticulate. So by considering the difference of different types of void volume, various densities are proposed.True density: It is defined as total volume of solids excluding all space greater than molecule diameter. True density can be measured with helium pycnometer.Bulk density: It is defined as total volume occupied by entire powder mass. It can be determined by placing previously sieved powder bulk into a graduated cylinder and measuring the volume in milliliters. Division of original weight and attended volume gives idea about bulk density.Tapped density: It is determined by placing graduated cylinder containing known weight of sample on tapped density apparatus and is operated for the fixed number of taps until a constant volume is attained. Ratio of total amount of substance taken to the final constant volume gives idea about tapped density. One needs to gain knowledge about the size and type of dosage form and is the most critical parameter for the low potency drugs. In most of the cases, two types of density are studied, namely, bulk density and tapped density.Following problems can be addressed related to density:With drugs having low density, the bulk becomes more and hence capsule formulation is quite difficult to formulate as capsule can incorporate limited volume.In development of tablet formulation, low-density drug creates difficulties as they are having low compressibility and hardness in tablet is difficult to achieve.If the difference of density is more between drug substances and excipients more, homogeneity in the formulation is difficult to achieve.Flow property of material can be affected by a number of factors including frictional forces, surface tension forces, electric forces, and van der Waals forces.Efficient flow of drug substance powder is needed for effective tablet formulation. The main reason behind inclusion of this parameter in preformulation is its linkage with other physical parameters like hygroscopicity and particle size and shape. Importance of flow property is even more when dose loading is more. Table 6 gives outline on correlation of flow properties of a material with moisture uptake at different humidity levels.In case of hygroscopic material, flow property of drug tends to deteriorate as the presence of absorbed moisture increases cohesiveness.Irregular particle size and nonuniform shape can also disturb normal flow property of drug.Relative humidity (%)Moisture uptake (%)Flowability10.30Free flowing100.24Free flowing100.25Less free flowing100.35Base of powder adheres to the container600.62Cake formationCorrelation between relative humidity, moisture uptake, and flowability.Normally, flow property of solid drug substance can be measured by Hausner ratio, Carr's index, and angle of repose, and in case of liquids or semisolid, rheology and thixotropy. Carr's compressibility index can be represented by the following formula.Carr's compressibility index=Tapped density-Bulk densityTapped density*100.E3Hausner's ratio can be represented by the following equation:Hausner's ratio=Tapped density/Bulk densityE4Table 7 provides the correlation between Carr's index, Hausner's ratio, and flowability.Carr's indexHausner's ratioFlowability5-151.05-1.18Excellent12-161.14-1.20Good18-211.22-1.26Fair-passable23-351.30-1.54Poor33-381.50-1.61Very poorGreater than 40Greater than 1.67Very poorCorrelation between Carr's index, Hausner's ratio, and flowability.Another way of measuring flow property is angle of repose, which provides the idea resistance to the movement of particle. It can be represented by the following formula:It is the maximum angle that can be obtained between height of pile and a horizontal plane. It gives a brief idea about internal cohesive and frictional levels. There are basically two types of methods that are available, which are as follows:Static angle of reposeFixed funnel methodFixed cone methodDynamic angle of reposeRotating cylinder methodTilting box methodAdvertisementExcipients are added along with the active pharmaceutical ingredient in formulations. Most excipients possess biological activity but having role in administration, mediating the release of the active component, and providing stability against degradation. However, inappropriate excipients can also give rise to inadvertent and/or unintended effects, which can affect the chemical nature, the stability, and the bioavailability of the API, and consequently, their therapeutic efficacy and safety. So study about interaction between active ingredient and inactive ingredient can provide idea about type of incompatibility and the justification behind the inactive ingredient selection [14].Change in organoleptic properties of formulation.Changes in in vivo performance of formulation, that is, dissolution.Decreased potency of active ingredient.Generation of toxic degradation product.Change in physical appearance of formulation, that is, color, phase conversion.In general, one can say that drug-excipient incompatibility may result in change in physical, chemical, microbiological, or therapeutic properties of formulation. In such an instance, active pharmaceutical ingredient and excipients interact without undergoing changes involving like breaking or formation of new bonds. The resulting drug product retains its original chemical properties but may involve changes such as alteration in physical properties. Such interaction results in changes like change in color, odor, flow properties, and sedimentation rate. Such an example of physical incompatibility is between tetracycline and calcium carbonate. It results in formation of insoluble complex with calcium carbonate, leading to slower dissolution and decreased absorption in the gastrointestinal tract [15].In such incompatibility, there is interaction of active pharmaceutical ingredient and excipient through chemical degradation pathway. The chemical reaction involves bond breakage or new bond formation to produce an unstable chemical entity. Chemical reaction may take place as hydrolysis, oxidation racemization, and Maillard reactions. The resulting changes are more deleterious than physical incompatibility. This type of incompatibility can be assessed by chromatographic studies. One of the classical examples of chemical incompatibility is exhibited by reaction of lactose with amino group of active pharmaceutical ingredient referred to as "Maillard reaction" and results into darkening of formulation with characteristic odor. Classical example is of a bronchodilator aminophylline, in which ethylenediamine moiety is reduced by lactose and as a result brown discoloration appeared in samples containing 1.5 (w/w) mixtures of aminophylline and lactose after storing at 60°C for 3 weeks [16].Such interaction is also referred to as biopharmaceutical interaction, but it differs from previously discussed incompatibilities in a way that interaction will take place once the formulation is administered into the body. Such type of incompatibility is associated with alteration in drug absorption in the body. In other way, one can say that interaction is taking place between excipient, active component, and physiological fluid. One of the classical examples of such incompatibility is interaction of enteric coated polymers, when administered along with antacids. In such an event, they dissolve prematurely and release the drug that is liable to acid degradation or may cause adverse effect in GI, that is, gastric bleeding associated with NSAIDs [17].There are specific methods that are employed to determine the existence of incompatibility between excipient and the active pharmaceutical ingredient. Out of all analytical techniques, thermal methods of analysis can provide most positive outcome. In association with thermal methods of analysis, spectroscopic techniques like X-ray diffraction and infrared spectroscopy can provide sideline assistance. High-performance liquid chromatography and thin-layer chromatography provide the more suitable way of studying chemical incompatibilities and provide qualitative and quantitative assessments.AdvertisementIt can be concluded that preformulation is a proactive phase that deals with transformation of new chemical entity into a safe, effective, and most importantly stable pharmaceutical formulation.1. Sigfridsson K, Nilsson L, Ahlqvist M, Andersson T, Granath AK. Preformulation investigation and challenges; salt formation, salt disproportionation and hepatic recirculation. European Journal of Pharmaceutical Sciences. 2017;104:262-272. DOI: 10.1016/j.ejps.2017.03.0412. Abet V, Filace F, Recio J, Builla JA, Burgos C. Prodrug approach: An overview of recent cases. European Journal of Medicinal Chemistry. 2017;127:810-827. DOI: 10.1016/j.ejmech.2016.10.0613. Lohar V, Singhal S, Arora V. Prodrug: Approach to better drug delivery. International Journal of Pharmaceutical Research. 2012;4(1):15-214. Hajnal K, Gabriel H, Aura R, Erzsébet V, Blanka SS. Prodrug strategy in drug development. Acta Medica Marisicensis. 2016;62(3):356-362. DOI: 10.1515/amma-2016-00325. Bhosle D, Bharame S, Gairola N, et al. Mutual prodrug concept: Fundamentals and applications. International Journal of Pharmaceutical Research. 2006;68(3):286-2946. Chabra N, Aseri ML, Padmanabhan D. A Review on Drug Isomerism and its Significance. International Journal of Applied Basic Medical Research. 2013;3(1):16-18. DOI: 10.4103/2229-516X.1122337. Smith SW. Chiral toxicology: It's the same thing...only different. Toxicological Sciences. 2009;110(1):4-30. DOI: 10.1093/toxsci/kfp0978. Black K, Raissy H. Chiral switching drugs of asthma and allergies: True benefit or marketing hype. Pediatric Allergy, Immunology, and Pulmonology. 2013;26(3):157-160. DOI: 10.1089/ped.2013.02959. Gohel MC. Overview on chirality and applications of stereo-selective dissolution testing in the formulation and development of drug. Dissolution Technologies. 2003;1(03):16-20. DOI: 10.1422/DT.00303P1610. Iqbal A, Sofia A, Zubair A, Ali SM, Sikorski M. Photo stability and photo stabilization of drugs and drug products. International Journal of Photoenergy. 2016;1-19. DOI: 10.1155/2016/813560811. Babak J, Inga B, Ole N, Steen HH. Investigation of racemization of the enantiomers of glitazone drug compounds at different pH using chiral HPLC and chiral CE. Journal of Pharmaceutical and Biomedical Analysis. 2008;46(1):82-87. DOI: 10.1016/j.jpba.2007.09.00412. Censi R, Di Martino P. Polymorph impact on the bioavailability and stability of poorly soluble drugs. Molecules. 2015;20:18759-18776. DOI: 10.3390/molecules20101875913. Chaurasia G. A review on pharmaceutical chiral formulation studies in formulation and development of new drug molecules. International Journal of Pharmaceutical Sciences and Research. 2016;7(6):2313-2320. DOI: 10.13040/IJPSR.0975-8232.7(6).2313-2320.14. Verma G, Mishra M. Pharmaceutical Preformulation studies in formulation and development of new dosage form: A review. International Journal of Pharma Research & Review. 2016;5(10):12-2015. Patel P, Ahir K, Patel V, Patel C. Drug-excipient compatibility studies: First step for dosage form development. The Pharma Innovation Journal. 2015;4(5):14-2016. Bharate SS, Bharate SB, Bajaj AN. Interactions and incompatibilities of pharmaceutical excipients with active pharmaceutical ingredients: A comprehensive review. Journal of Excipients and Food Chemicals. 2010;1(3):3-2617. Shadab MR, Ghaderi F, Hatami L. Investigation of possible Maillard reaction between acylcylol and dextrose upon dilution prior to parenteral administration. AAPS PharmSciTech. 2016;17(6):1491-1499. 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