CHAPTER - 1

Preformulation Studies

Molecular optimization of APIs (drug substances), crystal morphology and variations, powder flow, structure modification, drug-excipient compatibility studies, methods of determination.

MOLECULAR OPTIMIZATION OF APIs (DRUG SUBSTANCES)

Since long the physical properties of optimized active pharmaceutical ingredients (API) such as bulk properties, surface/ interfacial properties, and mechanical properties are important for manufacturing of drug product. The APIs with these challenging properties can produce the issues, such as inconsistent powder feeding, de-mixing of blends, variable die-filling, and punch sticking. Ultimately these produce unacceptable final tablet quality attributes. Inefficient processes and high batch rejection rates also affects environmental impacts. Some of these effects may not be directly affect the patient. The processes can be costlier or can cause problems with the availability of the products. Such processes are not robust. These processes show high degree of rejections or are difficult to be scaled-up and their technology are difficult to be transferred, the ability to tailor the physical properties of APIs can have great possibility to cause various problems for manufacturing of drug products. This helps both the conventional batches and advanced continuous manufacturing processes. The second one, that is, the continuous manufacturing process has gained priority as an emerging technology. These are considered and promoted by the regulatory agenciies[1-3], and attracted the interest of academics, and research interests[4]. One way to manage the physical properties of an API is the selection of an appropriate crystal form. The physical or chemical stability and the morphology of the drug product depend mainly on the selection of an appropriate polymorph, hydrate or solvate, salt, or co-crystals of the API. However, this is not always true for the conventional, or targeted *in vivo* behavior. When the selection of an alternative solid form is not an option, by adjusting the process parameters of crystallization, such as rate of supersaturation, temperature, concentration, solvent system, mixing parameters, such as, wet-milling or seed size/quantity, mixing speed, etc., can produce the improved physical properties of the drug products. However, this is not a universal solution, and in certain cases may

cause slightly positive results. There is another method of spherical crystallization. This technique involves intentional controlled agglomeration process during isolation/drying. Such process can greatly improve physical properties of drug product[5-10].

Emulsion based crystallization process can produce spherical agglomerations of the API[11,12,] this is another method. A recent study reveals that by using solvent diffusion, or by changing the pH, the quasi-emulsification can cause spherical crystallization[13]. In general, the spherical crystallization could not be commercially feasible because of the problems such as volumetric productivity, managing solubility in complex ternary solvent systems. Process complexity of developing and scaling multi-phase slurries, and the difficulty in maintaining intact particles during isolation and drying of powders.

Moreover, there is another class of pharmaceutical materials evolved which do not show the properties of well-defined crystalline materials. With ever-increasing knowledge of biological systems that provides novel biological targets, the pharmaceutical industry is developing new molecules with different modalities, such as, macrocycles, peptides, protein degradomers, RNA, siRNA[14]. In most cases, these do not comply with Lipinski's rule of five for drug-like properties[15]. New molecules today can frequently be large (>500 Da). New molecular entities today can be lipophilic (poorly-water solubles)[16,17] and show a lack of propensity for crystallization[18,19]. Properties of these classes of compounds render them difficult to be isolated and stabilised. Therefore, these become challenging, if not impossible, to formulate in conventional drug product processing routes.

An important and more universal route to optimise API properties (both crystalline materials, and non-crystalline materials or a poorly defined crystalline materials) is to incorporate the non-active components during formation of particles and/or subsequent isolation and drying to provide coprocessor API[20]. Many pharmaceutical companies agree that despite the promises posed by co-processed API, regulatory uncertainty for co-processed API inhibits commercial implementation.

Co-processed API can be defined as *a drug substance, manufactured in a drug manufacturing facility, that contains the API in addition to one or more non-covalently bonded, non-active component, and differs from salts, solvates and/or crystals.* Co-processed APIs differ from salts, solvates and crystals because API and non-active components do not exist in the same crystal lattice and do not always bear a defined stoichiometry. Non-active component is defined as *a component such as a carrier, additive, or other excipient that is non-covalently bonded with the API and is included in the co-processed API to improve the physical properties.* The non-active components commonly cited in the literature are compendial excipients, with a smaller subset of cited

work involving GRAS materials, and an even smaller subset of novel excipients. In case of novel excipients, safety/toxicology information, the route of administration, dose and CMC information would require to be considered and provided in regulatory submission as appropriate.

The proposed definition of co-processed API is in the line with the ICH Q7 definition of an API or drug substance. This includes any substance or mixture of substances to be used in the manufacture of a drug product. When used in the production of a drug, becomes an active ingredient of the drug product[21]and the ICH Q7 Q & A clarifies that mixtures with "the addition of substances to an API to stabilise the API" can be classified in the regulatory filing as an API[22]. A co-processed API may improve the stability of the drug substance. If polymorphic. form is stabilised by the presence of the non-active components[23-25]. Moreover, it is suggested that an additional appropriate justification to include non-active components in a drug substance. It is for the purpose of optimization of physical properties of API. There are some examples of regulatory acceptance of inclusion of non-active components in a commercial drug substance with justification based on stabilisation of an amorphous form[26] or improvement of physical properties[27]. ICH Q7 recognises that in some cases physical properties such as particle size distribution, bulk density, and tap density, may be critical for a drug substance, further emphasising the importance of the optimization of API properties and potential benefits of co-processed APIs.

Usually, the co-processed API is a formulation-ready entity that can be appropriately characterized and reproducibly meet the required specifications for the drug substance critical quality attributes (CQAs). Co-processing at a drug manufacturing facility is beneficial with respect to the equipment and controls are necessary for solvent-based manufacturing such as damage limiting construction and utilises for operation under inert atmosphere, required to generate, isolate, and dry the co-processed API generally do not exist at drug product manufacturing facilities. In fact, for many co-processing methods, co-processed API can be produced 'in-the-flow 'of existing drug substance manufacturing. That is, before addition of non-active components the API do not require isolation and co-processing does not require any added unit operations or even extended time cycle. Moreover, the designing of co-processed API as a drug substance from a regulatory perspective allows the potential to support a rework/reprocessing procedure of the co-processed API. It suggests an approach for the API to expiry dating that assures quality. These allow greater supply chain flexibility and reducing a costly discard.

There have been appreciable developments in regulatory considerations for APIs with special circumstances, for example, regulatory agencies have been more receptive to introducing excipients during commercial drug substance processes where there are either physical or chemical stability challenges[28].

Moreover, the allowance to extend the hold-time of amorphous solid dispersions following an end-to-end (in-series) stability testing protocol is encouraging[29]. The FDA's recent cocrystal guidance states the reason for selecting a cocrystal in place of traditional crystalline API. That is, "co-crystals can be made to improve the bioavailability and stability of the drug product and to improve the processability of APIs during the manufacture of drug product[30]. This statement accepts that the processability of the APIs should be considered as an important factor along with bioavailability. The ability to use more complex multi-component materials isolated as drug substances can allow this goal to be realised.

These processes use typical drug manufacturing equipment, with limited logistical and technological hurdles for quick commercial implementation. The commercial application of the co-processing technologies requires similar regulatory treatment on the following topics:

1) The definition of co-processed API and proposal to manufacture co-processed APIs at a drug substance facility as per ICH Q7,
2) Primary stability and expiry dating expectations for a co-processed API,
3) Characterisation and release test expectations for a co-processed API.
4) It is desired that collaboration with global regulatory agencies will be required to fully capture the implications of pursuing co-processed APIs and identifying a route for the pharmaceutical industry to cater these innovative processes forward in development and commercialisation.

CRYSTAL MORPHOLOGY AND VARIATIONS

In 1669 when the Danish scientist Niels Steensen, studying in Florence the quartz and hematite crystals from Elba Island, suggested the first law of crystallography (the constancy of the dihedral angle) and mechanism of face growth (layer by layer). Thereafter the interest for crystal habit of minerals has been observed. H.J. Scheel[31] has described the history on this topic and crystallization with short account on crystal morphology. Crystal habit drew the attention of the great scientist like Kepler, Descartes, Hooke, Huygens. Since beginning of crystallography as science, crystal habit has become relevant scientifically. At the end of the 18th century the study of calcite crystals leads to formal stating of the first theory on crystal structure and discovery of the second law (rational indices). In the first part of 19th century the study of crystal habit led to the development of the concept of symmetry and derivation of the 32 crystal classes.

From about 1950 onwards, the interest for crystal growth becomes more and more increasing due to the role of crystals in all kind of industry and to the discovery of relevant properties of new crystalline compounds. The crystal habit has been receiving a growing attention due to theoretical interest and

industrial needs. The Donnay-Harker principle is exclusively crystallography. Computer facilities have promoted tremendously in any kind of calculation, necessary in the different sectors of crystal growth, allowing progress in theoretical approach and sophisticated simulations. These are now a routine practice.

When equilibrium attains between a crystalline phase and its surroundings, the statistical amount of growth units exchanged between the two phases remains the same and does not change with time. This states that the crystallised volume remains constant, but nothing is specified about many important questions:

i) What is about the surface of the crystals, that is, how large is its extension and what are the (hkl) forms entering the equilibrium shape (E.S.) of the crystal?

ii) What is the difference, if any, between the stable E.S. of a crystal immersed either in a finite mother phase or in an infinite one and the unstable shape which obtains when the activation energy for nucleation is reached?

iii) How the E.S. does change when some adhesion sets up between the crystal and a solid substrate?

iv) How can be the solvent and the impurity concentration affect the E.S.?

Factors influencing the crystal habit:

The morphology, we mean the set of (hkl) crystal forms, occurs in a crystal independently on the surface areas. In many industrial sectors the crystal-habit change is necessary to

- Prevent crystal-caking,
- Filter crystal precipitates,
- Obtain more convenient crystal products (shape, size, size separation, purity, quality),
- Make easy storage and package, etc.

The procedures to study the crystal habit change are well established:

(1) Experimental crystal habits, and (2) growth in different solvents, are compared to the theoretical one, which may be obtained by calculations with different available methods (BFDH; PBC-attachment energy-connected nets); the analysis or by growing the crystal from the vapour phase, in which the fluid-solid and fluid-fluid interactions are negligible. As the crystal-solution interface is the critical site to face the growth and crystal habit, all the disposable devices are applied to the study of surface. They are usually classified into two main categories:

i) *Internal factors:* the crystal structure, on which the surface structures (i.e., the profiles) of the faces depend; the crystal defects;

ii) *External factors*, which act from the "outside" are: supersaturation, nature of solvent, solution composition, impurities, physical conditions (temperature, solution flow, electric and magnetic field, microgravity, ultrasound, etc.)

iii) There are also *mixed factors,* such as the free energy of crystal surfaces and edges, which depend both on crystal surface structure (an internal factor) and growth environment (external one).

Surface structure

Each crystal face has a specific surface structure, which controls its growth mechanism. The surface of a F face is not perfectly flat and smooth. The face is covered by steps and other features (hillocks), the growth rate of the face and its development. Indeed, layer growth is possible when the edge energy of a 2D nucleus is positive[32]. Surface features (dislocation activity, step bunching) and parameters (step speed, hillock slope) are sensitive to supersaturation, impurities and behave in different ways at low and high supersaturation, with linear and non-linear dependence[33]. Surface phenomena and morphology have been recently reviewed[34-36]. AFM has enormously enlarged the research field, as it allows to observe the surface features of the growing faces ex situ and in situ at a molecular level.

- **The α factor and the roughening transition**

  The concept of α factor was brought in as a measure of roughness of a surface and of its probable growth mechanism. Knowledge of α is mostly useful, however it may not be sufficient, as noticed for several alkanes. These show the same α in different solvents yet have different growth mechanisms[37] such as faces of succinic acid grown from water and isopropyl alcohol (IPA). Each face has the same α value in both solvents, nevertheless the growth rates are appreciably lower in IPA than in water, because of different efficiency of hydrogen bond in IPA and water molecules[38]. With increasing temperature, the α factor decreases and may reach values lower than 3.2. In that case the surface loses its flatness, becomes rough and grows by a continuous mechanism. The transition occurs at a definite roughening temperature which is characteristic for each face. Below the TR, the faces are straight, above it. They become round off even if supersaturation is very low[39].

- **Kinetic roughening**

  Beside thermal roughening, a surface may undergo a kinetic roughening. This occurs below the roughening temperature when supersaturation exceeds the critical value. In that case the sticking fraction on the surface is so high and critical two-dimensional nucleus so small that the surface

becomes rough and grows through a continuous mechanism. This behaviour was observed on the faces of NaCl in aqueous solutions and in naphthalene crystals, which become fully rounded-off when σ attains 1.47%. in toluene solvent. The same does not occur with hexane, due to structural dissimilarity of hexane molecules with respect to naphthalene. Four criteria used to identify the beginning of kinetic roughening have been studied by Monte Carlo simulations on a Kossel surface, which lead to different values of the critical driving force[40].

- **Polar crystals**

  In polar crystals a slice dhkl may present a dipole moment. In that case, a correction term, E_{corr}, should be brought into the expression of E_{att} to maintain constant the value:

  $$E_{cr} = E_{att} + E_{slice} + E_{corr}$$

  Where, Ecorr = 2 π μ 2 / V,

  V = the volume of the primitive cell and

  μ = the dipolar moment of the slice.

  The surfaces of the two opposite faces (hkl) and (<u>hkl</u>), being structurally similar can interact in a selective way with the solvent and impurity molecules. The final result is a development of these faces, which may lead to the occurrence of only one form. In the case of water molecules, these faces are selectively adsorbed on the opposite faces since they have different surface distribution of sulphite ions. The structural differences can be so great that the two opposite faces may grow with different mechanism.

- **Surface with AFM (Atomic Force Microscopy)**

  AFM has become a routine technique in laboratories where crystal-growth experiments are studied. Most experiments are carried out in static conditions, some in dynamic conditions. For example, besides proteins, one of the most studied compounds is calcite. The cleavage form grows via monomolecular steps, which are affected by anion and impurities present in calcite. AFM has been used to assess the stability of the faces of NaCl in pure and impure aqueous solutions and in the attempt to solve the problem of surface reconstruction. Through Atomic Force Microscopy (AFM) investigation of the faces of Potassium Dihydrogen Phosphate (KDP), the dependence of macro-steps and hillocks on β-form was measured and the new values of the step edge energy, kinetic coefficients and activation energies for the step motion were calculated, confirming the models of Chernov and van der Eerden and Müller-Krumbhaar[41]. In studying the influence of organic dyes on potassium sulphate the link between the surface features at the nanoscale level and the macroscopic habit change was proved. To sum up, the AFM analysis allows to seize

local details of surface structure and their evolution in real time, brings a lot of information, but has the drawback as it does not permit to have a large-scale glance of the face, so it has to be integrated with other instrumental, optical or X-ray, techniques.

Crystal defects

Defects in crystals are easily and usually observed. It is not necessary to emphasize the role of screw dislocations in crystal growth. In case of edge dislocations, these could affect the growth rate since a strain energy is related to the Burgers vector and the growth rate increases. Combined research on the effect of dislocations on crystal growth with in-situ X-ray topography was done on Adenosine Dihydrogen Phosphate (ADP) crystal. Edge dislocations are proved to be inactive in step generation on the ADP face, whereas the screw dislocations are active. When a dislocation line emerges on a given (hkl) face, the face grows at higher rate than the other equivalent ones and therefore decreases its morphological importance with respect to the others. In the crystals of cubic symmetry, the habit may change from cube to tetragonal prism or square tablet. When a screw dislocation crosses an edge, it becomes inactive. On the other hand, currently it is stated that if the growth rate increases, the defect density, also increases; this is supported by Monte Carlo simulations. That is, the large crystals having a high degree of structural perfection can be obtained with the method of "rapid growth". This consists of overheating a supersaturated solution, inserting a seed conveniently shaped and strongly stirring the solution submitted to a temperature gradient. This method allows to prepare in short time very large crystals of technologically important compounds as KDP and Deuterated Potassium Phosphate (DKDP) up to 90 cm long and nearly free of dislocations. Crystals grown with the traditional method at low temperature are smaller, rich in striations and dislocations, originated by liquid inclusions. Large perfect crystals can be fast grown also from highly concentrated boiling water solutions. The method has been successfully applied to some compounds, as KDP, $Pb(NO_3)$, $K_2Cr_2O_7$. Due to the high growth rates and β-form of the crystal habit becomes equidimensional [42].

POWDER FLOW

Knowledge of the flow properties of a powder or a bulk solid is necessary to design silos and other bulk solid handling equipment so that no flow problems (flow obstructions, segregation, irregular flow, flooding, etc.) can occur. Furthermore, quantitative information regarding flowability of bulk products is required as a part of comparative tests (such as, the effect of flow agents or other additions on flow behaviour) and quality control. The flow properties depend on several parameters, such as

- Particle size distribution,

- Particle shape,
- Chemical composition of the particles,
- Moisture,
- Temperature.

On the basis of all of these parameters, it is not possible to determine theoretically the flow behaviour of bulk solids. This would have been possible, even the expense for the determination of all parameters of influence would be very high. Thus, it is necessary, and also simpler, to determine the flow properties in appropriate testing devices. All types of solids are called bulk solids, powders, or granulates. In the following the general expression "bulk solid" is used for all these products.

Stresses in bulk solids Figure 1.1 shows a bulk solid element in a container (assumptions: infinite filling height, frictionless internal walls). In the vertical direction, positive normal stress ($\sigma_v > 0$, compressive stress) is exerted on the bulk solid. If the bulk solid behaves like a Newtonian fluid, the stresses in the horizontal and vertical direction (and in all other directions) would be of equal magnitude. In reality the behaviour of a bulk solid is quite different from that of a fluid, so that the assumption of analogies is often misleading. Within the bulk solid (Figure 1.1) the horizontal stress, σ_h, is a result of the vertical stress, σ_v, the resulting horizontal stress is less than the vertical stress exerted on the bulk solid from the top. The ratio of horizontal stress to vertical stress is the stress ratio, K, known as λ.

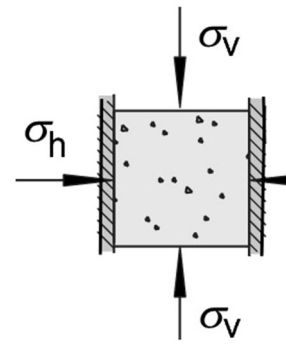


Fig.1.1 Element of bulk solid.

In analogy to solids– a bulk solid of different stresses can be found in different cutting planes. Stresses in cutting planes other than the vertical and the horizontal can be analysed using a simple equilibrium of forces. No shear stresses τ are exerted on the top or bottom surface of the bulk solid element in Figure 1.1; that is, the shear stresses in these planes are equal to zero. No shear stresses can act at the lateral walls, since the lateral walls were assumed as frictionless. Thus, only the normal stresses shown act on the bulk solid from outside. Using a simple equilibrium of forces at a volume element with triangular cross-section cut from the bulk solid element shown in Figure 1.1, the normal stress, σα, and the shear stress, τα, acting on a plane inclined by an arbitrary angle α, can be calculated. After some mathematical transformations, which need not be considered here, it follows that:

$$\sigma_\alpha = \frac{\sigma_v+\sigma_h}{2} + \frac{\sigma_v-\sigma_h}{2}\cos(2\alpha) \qquad \text{.....(1)}$$

$$\tau_\alpha = \frac{\sigma_v - \sigma_h}{2} \sin(2\alpha) \quad \text{.....(2)}$$

The pair of values, σ_α, τ_α, can be calculated according to equations (1) and (2) for all possible angles α, can be plotted in a σ,τ-diagram (normal stress, shear stress - diagram); If one joins all plotted pairs of values, a circle emerges; i.e., all calculated pairs of values form a circle in the σ,τ-diagram.

This circle is called "the Mohr stress circle". Its centre is located at,

$\sigma_m = (\sigma_v + \sigma_h)/2$ and $\tau_m = 0$.

The radius of the circle is $\sigma_r = (\sigma_v - \sigma_h)/2$.

The Mohr stress circle represents the stresses on all cutting planes at arbitrary inclination angles α, that is, in all possible cutting planes within a bulk solid element. Since the centre of the Mohr stress circle is always located on the σ-axis, each Mohr stress circle has two points of intersection with the σ-axis. The normal stresses defined through these points of intersection are called the principal stresses, whereby the larger principal stress, the major principal stress is designated as σ_1 and the smaller principal stress, the minor principal stress is designated as σ_2. If both principal stresses are given, the Mohr stress circle is well defined.

In the Fig 1.1 both the horizontal and the vertical plane are free from shear stresses ($\tau = 0$) and are thus principal stress planes. In this case, the vertical s_t products are "poorly flowing"; stress, σ_v, which is greater than the horizontal stress, σ_h, is the major principal stress, σ_1, and the horizontal stress, σ_h, is the minor principal stress, σ_2.

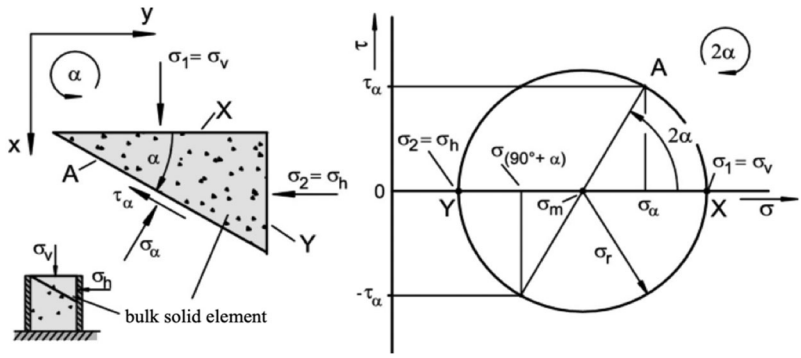


Fig.1.2 Force equilibrium on an element of bulk solid, the Mohr stress circle.

An important qualitative result of the above analysis is that shear stresses can occur in bulk solids at rest. This is impossible for a Newtonian fluid at rest (in contrast to Newtonian fluids, bulk solids can have sloped surfaces even at rest). Therefore, a representation of the stresses (fluids: pressures) in different cutting planes of a Newtonian fluid at rest in a σ, τ-diagram would yield a stress circle with the radius zero (equation (2) with $\sigma_h = \sigma_v$ yields $\tau_\alpha = 0$). From

the explanation above it follows that the state of stress in a bulk solid cannot be completely described by only a single numerical value. On the basis of the actual load acting on a bulk solid element, the corresponding Mohr stress circle (Fig 1.2) can have a smaller or a larger radius, a centre at a lesser or greater normal stress, and hence also different principal stresses, σ_1 and σ_2. In principle, at a given major principal stress, σ_1, stress circles with different values for the lowest principal stress, σ_2 are imaginable. Therefore, a stress circle is defined clearly only if at least two numerical values are given, i.e., σ_1 and σ_2. In summary, the following can be stated with regard to the stresses acting in bulk solids:

- A bulk solid can transmit shear stresses even if it is at rest.
- In different cutting planes different stresses are acting.
- Stress conditions can be represented with Mohr stress circles[43-45].

Flowability

Uniaxial compression test

The phrase "good flow behaviour" commonly refers to that a bulk solid can flow easily. If they experience flow obstructions or consolidate during storage or transport, the products "poorly flows". In contrast to these qualitative statements, a quantitative statement on flowability is possible only when one can use an objective characteristic value. This considers those physical characteristics of the bulk solid that are responsible for its flow behaviour. "Flowing" means that a bulk solid is deformed plastically due to the loads acting on it. The magnitude of the load necessary for flow is a measure of flowability. This will be demonstrated first with the uniaxial compression test. Figure 1.3 shows a hollow cylinder filled with a fine-grained bulk solid (cross-sectional area A; internal wall of the hollow cylinder assumed as frictionless). The bulk solid is loaded by the stress σ_1, the consolidation stress, in the vertical direction.

The more the volume of the bulk solid specimen is reduced, the more compressible the bulk solid becomes. In addition to the increase in bulk density from consolidation stress, one will observe also an increase in strength of the bulk solid specimen. Hence, the bulk solid is both consolidated and compressed through the effect of the consolidation stress.

After consolidation, the bulk solid specimen is relieved of the consolidation stress, σ_1, and the hollow cylinder is removed. If subsequently the consolidated, the cylindrical bulk solid specimen is loaded with an increasing vertical compressive stress, the specimen will break (fail) at a certain stress. The stress causing this failure is called *compressive strength* or *unconfined yield strength*, σc (another common designation is f_c). In bulk solids technology one calls the failure "incipient flow", because at failure, the consolidated bulk solid specimen starts to flow. Thereby the bulk solid dilates

somewhat in the region of the surface of the fracture, since the distances between individual particles increase. Therefore, incipient flow is plastic deformation with decrease of bulk density. Since the bulk solid fails only at a sufficiently large vertical stress, which is equal to the compressive strength, there must exist a material-specific yield limit for the bulk solid. When this yield limit is reached, the bulk solid starts to flow. The yield limits of many materials (e.g. metals) are material dependent. However, the yield limit of a bulk solid is dependent also on its stress history, i.e., previous consolidation: The greater the consolidation stress, σ_1, the greater the bulk density, ρ_b, and unconfined yield strength, σ_c. Uniaxial compression tests conducted at different consolidation stresses, σ_1, leads to different pairs of values (σ_c, σ_1) and (ρ_b, σ_1).

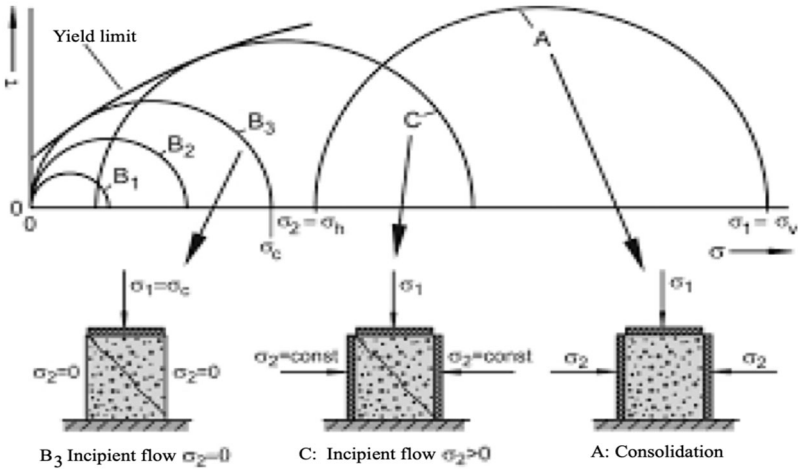


Fig.1.3 Measurement of unconfined yield strength in a σ, τ-diagram.

Time consolidation (caking)

Some bulk solids increase in strength if they are stored for a longer time at rest under a compressive stress (e.g. in a silo or an intermediate bulk container). This effect is called time consolidation or caking. Time consolidation can be determined with the test. For this one the loads the specimen with consolidation stress, σ1, not only for a short moment, but for a defined period of time, t_1. Then the unconfined yield strength is determined following the principle. This shows the flow function $\sigma_c(\sigma_1)$ of product A as previously (unconfined yield strength without influence of time consolidation, that is, for a storage period t = 0). This result is true for many bulk solids, but not for all. There are bulk solids which undergo no or only very slight consolidation over time, i.e., σ_c does not increase, or increases only very slightly with increasing storage period, t (e.g. dry quartz sand). Other bulk solids undergo a large increase in unconfined yield strength after storage

periods of only a few hours, whereas after longer storage periods their unconfined yield strength does not increase further. These differences are due to the different physical, chemical, or biological effects that are the causes of consolidation over time, for example. chemical processes, crystallisations between the particles, enlargement of the contact areas through plastic deformation, capillary condensation, or biological processes such as fungal growth.

With measurement of time consolidation, a "time-lapse effect" is not realisable; that is, one must store a bulk solid specimen at the consolidation stress, σ_1, for exactly that period of time for which one would like to get data on time consolidation. Without such a test no quantitative statement can be made regarding time consolidation.

Practical determination of flow properties

The flow behaviour has been explained in a simplified way by using the uniaxial compression test as a model. The use of the uniaxial compression test with fine grained, cohesive bulk solids is problematic, because one obtains unconfined yield strength values that are too low[46], and preparation of the hollow cylinder to obtain frictionless walls is very time-consuming. In addition, further important parameters such as, internal friction and wall friction cannot be determined with this test. It is, however, an appropriate measurement technique for the measurement of the time consolidation of coarse-grained bulk solids. In order to measure the flow properties of fine-grained bulk solids, in advanced bulk solids technology so-called shear testers are used. In the following first the principle of shear testing is outlined. Afterwards, the translational shear tester introduced by Jenike around 1960[47-49] and the Schulze ring shear tester[50,51].

Shear test procedure (yield locus)

The goal of a shear test is to measure the yield limit of a consolidated bulk solid. The yield limit is called *yield locus* in bulk solids technology. For a shear test, a bulk solid specimen is loaded vertically by a normal stress, σ (Figure 1.4a). Then a shear deformation is applied on the specimen by moving the top plate with a constant velocity, v. This results in a horizontal shear stress, τ (Figure 1.4.b). With increasing shear stress the resultant force, F_R, acting on the bulk solid specimen, increases. When a point of a yield locus is measured, in analogy to the uniaxial compression test, two steps are necessary: (1) First the bulk solid specimen is consolidated, what is called "pre-shear". (2) Subsequently a point of the yield limit is measured. This step is called "shear" or "shear to failure".

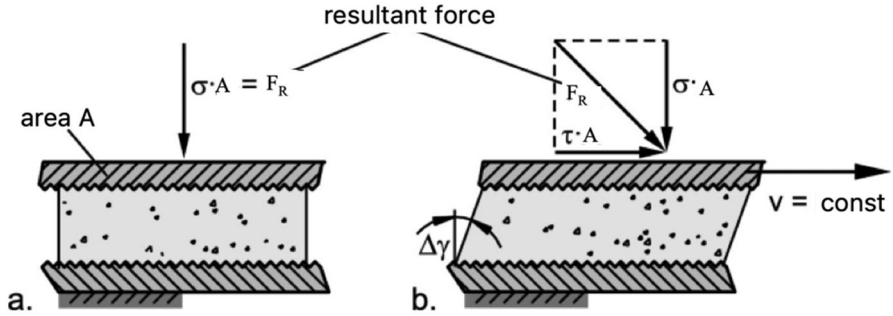


Fig.1.4 Bulk solid specimen: a. initial loading with normal stress σ; b. shear deformation (velocity v = const).

For pre-shear the bulk solid specimen is loaded in the vertical direction by a well-defined normal stress, $\sigma = \sigma_{pre}$. Then, the specimen is sheared. At the beginning of pre-shear, the shear stress τ increases with time as shown in the left diagram in Figure 1.4. With time the curve of shear stress vs. time becomes flatter, and finally the shear stress remains constant even though the specimen is sheared further. The constant shear stress is called τ_{pre}. After constant shear stress has been attained, neither shear resistance (and strength) nor bulk density increases further. Thus, the bulk solid specimen is sheared at constant normal stress, σ, constant shear stress, τ, and constant bulk density, ρ_b. The flow, or plastic deformation, occurs at constant bulk density. This type of flow, attained at pre-shear, is called steady-state flow. The state of the bulk solid after steady-state flow is attained is called "*critically consolidated with respect to normal stress, σ_{pre}*". The characteristic stress for this consolidation – the major principal stress σ_1 – will be considered later. The bulk density, ρ_b, and the shear stress, τ_{pre}, attained at steady-state flow are characteristic for the applied normal stress at pre-shear, σ_{pre}. In principle, an identical state of consolidation, characterised by the same bulk density, ρ_b, and the same shear stress, τ_{pre}, will be attained with other specimens of the same bulk solid pre-sheared under the same normal stress, σ_{pre}. After the bulk solid specimen has been consolidated by the pre-shear procedure, the shear deformation is reversed until the shear stress plot of shear stress vs. time; yield locus, τ, is reduced to zero. The pair of values of normal stress and shear stress at steady-state flow (σ_{pre}, τ_{pre}) is plotted in a normal stress - shear stress diagram (σ,τ-diagram, Figure 1.5 right). Point (σ_{pre}, τ_{pre}) is called the "pre-shear point"[52].

After pre-shear the bulk solid specimen in the shear cell is defined as a critically consolidated specimen.

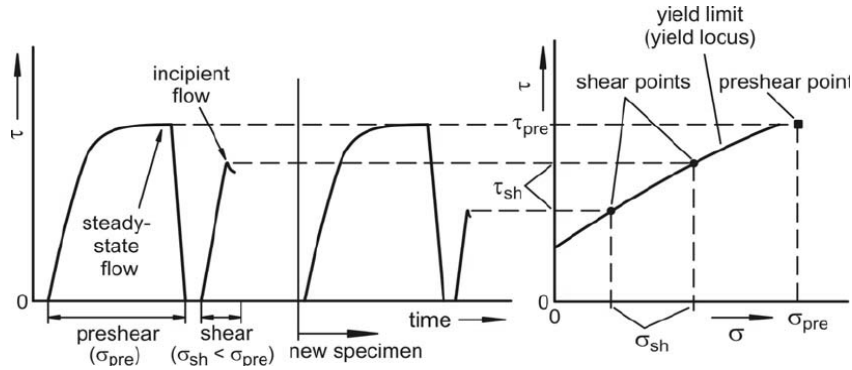


Fig 1.5 Plot of shear stress vs. time; yield locus.

The second step of the test procedure – shear or shear to failure – is discussed next. For shear to failure the normal stress acting on the specimen is decreased to a value σ_{sh}, which is less than the normal stress at pre-shear, σ_{pre}. Had the specimen been pre-sheared under the lower normal stress, σsh, and not under σpre, its bulk density and strength would have been less. Since the specimen was pre-sheared under the greater normal load, σ_{pre}, it was consolidated more than it would have been with the lower normal load, σsh. If the consolidated specimen is sheared under the normal stress σsh < σpre, it will start to flow (fail) when a sufficiently large shear force, or shear stress, is attained.

At that point particles start to move against each other. The material will start to dilate (decrease in bulk density) and shear resistance and thus shear stress will decrease. The maximum shear stress 15 characterizes incipient flow. The corresponding pair of values (σ_{sh}, τ_{sh}) is a point of the yield limit of the consolidated specimen in the σ,τ-diagram. Such a point is called a *shear point* or a *point of incipient flow*. To measure the course of the yield locus, several of the tests described above must be performed, where the specimens first must be consolidated at identical normal stress, σ_{pre} (pre-shear). Then, the specimens are sheared (failure) under different normal stresses, $\sigma_{sh} < \sigma_{pre.}$ As outlined above, by pre-shearing at identical normal stress, σ_{pre}, each specimen reaches the same state of consolidation. Each test yields the same pre-shear point (σ_{pre}, τ_{pre}), and one individual shear point (σ_{sh}, τ_{sh}) in accordance with the different normal stresses, σ_{sh}, applied at shear. The yield locus follows from a curve plotted through all measured shear points.

Yield locus

The parameters which describe the flow properties can be determined from the yield locus (Figure 1.6). The relevant consolidation stress σ_1 is equal to the major principal stress of the Mohr stress circle which is tangential to the yield locus and intersects at the point of steady state flow (σ_{pre}, τ_{pre}). This stress

circle represents the stresses in the sample at the end of the consolidation procedure (stresses at steady state flow). It corresponds to the stress circle at the end of consolidation at the uniaxial compression test (Figure 1.6). The unconfined yield strength, σ_c, results from the stress circle which is tangential to the yield locus, and which runs through the origin (minor principal stress $\sigma_2 = 0$). This stress circle represents a similar stress state as the one which prevails in the second step of the uniaxial compression test. In contrast to the uniaxial compression test the unconfined yield strength, σ_c, has to be determined on the basis of yield locus and does not follow directly from the measurement. It may be noted that the analogy between the uniaxial compression test and the shear test is used here for the explanation of the yield locus. In reality, the stress circles at uniaxial compression and at steady state flow are not exactly the same, and a uniaxial compression test usually results in a smaller unconfined yield strength than a shear test[53]. A straight line through the origin of the σ,τ-diagram, tangent to the greater Mohr circle (steady-state flow), is the effective yield locus as defined by Jenike (broken line in Figure 1.6). It encloses the σ-axis with the angle φ_e (effective angle of internal friction). Because the largest Mohr stress circle indicates a state of steady-state flow, the angle φ_e can be regarded as 0, right).

A measure of the internal friction at steady-state flow. This angle is required for silo design according to Jenike's theory. If several yield loci are measured at different stress levels, that is, with different normal stresses at pre-shear, σ_{pre}, each yield locus represents another state of consolidation and another bulk density. The above-mentioned flow properties (unconfined yield strength, effective angle of internal friction) can be indicated as a function of the consolidation stress, σ_1, where bulk density and unconfined yield strength are plotted vs. the consolidation stress.

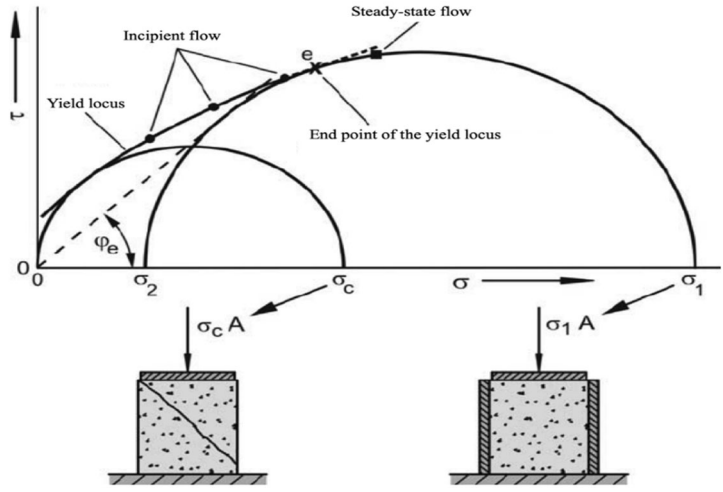


Fig.1.6 Yield locus, analogy to uniaxial compression test.

Time consolidation

Before time consolidation can be measured, a yield locus must be determined at the same consolidation stress. The time consolidation, which describes the increase of the unconfined yield strength with time during storage at rest, is measured with a shear tester similar to the measurement of a yield locus. First a bulk solid specimen is pre-sheared (consolidated). After pre-shear the specimen is stored for a period, t, under the vertically acting normal stress, σ, which is selected to be equal to the consolidation stress, σ1, of the corresponding yield locus. This ensures that during the consolidation period the same major principal stress = consolidation stress, σ_1 acts on the specimen as during steady-state flow at pre-shear.

After the time consolidation period t the specimen is sheared to failure. For this, a vertical normal load, σsh < σ1, is selected. As with shear without time consolidation (measurement of a point of a yield locus), so also after time consolidation will one observe a shear stress maximum. If consolidation time affects the bulk solid under consideration, after the consolidation period the shear stress maximum will be larger than it would have been without a consolidation period between pre-shear and shear.

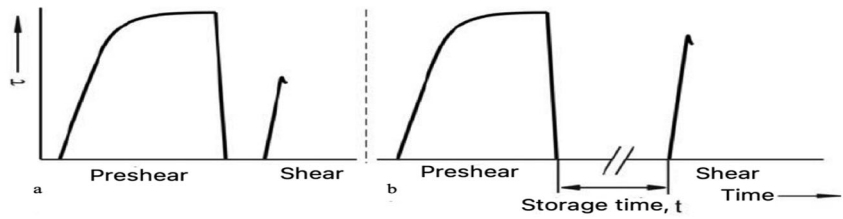


Fig.1.7 Shear stress vs. time at shear; with (a) and without (b) time consolidation.

The maximum shear stress, τ, is a point of a yield limit, which is valid for the applied storage period, t, and called a "time yield locus". Figure 1.7 shows a yield locus and two-time yield loci obtained for different consolidation periods, t_1 and t_2. The yield locus can also be regarded as a time yield locus for t = 0.

With the measured shear points, a time-yield locus can be approximated similarly to the approximation of a yield locus. Compared to the yield locus, the time yield locus is shifted towards greater shear stresses, τ (if the bulk solid shows an increase of strength with time). The unconfined yield strength, σc, is determined in the same way as for a yield locus by drawing a Mohr stress circle through the origin and tangent to the time yield locus. In Figure 1.7 the values of the unconfined yield strength for the consolidation periods, t_1 and t_2, are designated as $\sigma_c(t_1)$ and $\sigma_c(t_2)$. Time-yield loci can be determined for different storage periods (consolidation periods). Each time yield locus is valid for only one consolidation period and one consolidation stress. If the

strength of the bulk solid increases over time, the time-yield loci will be shifted towards larger values of τ as the consolidation period, t, increases (Figure 1.7, $t_2 > t_1$).

Wall friction

Wall friction is the friction between a bulk solid and the surface of a solid, such as, the wall of a silo or a bin. The coefficient of wall friction or the wall friction angle is important for both silo design for flow and silo design for strength, but also for the design of chutes and other equipment, where the bulk solid will flow across a solid surface. Knowing the wall friction angle, it is possible to decide whether or not the polishing of the wall surface or the use of a liner would have advantages in the flow of the bulk solid. The principle of a wall friction test, where the kinematic angle of wall friction is determined, is shown in Figure 1.8. The bulk solid specimen is subjected to a vertical normal stress. The normal stress acting between bulk solid specimen and wall material is called the wall normal stress, σ_w.

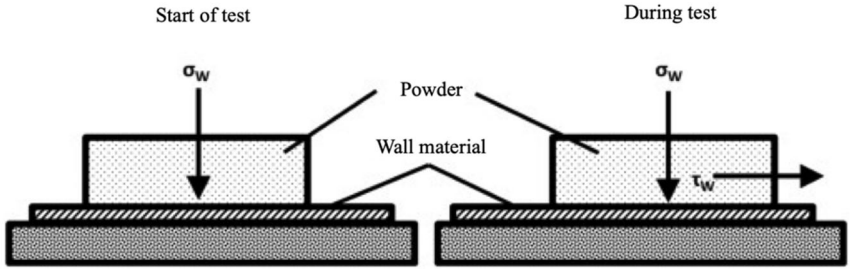


Fig.1.8 Principle of a wall friction test.

The bulk solid specimen is then shifted relative to the wall material surface with a constant velocity, v. This process is called shear (similar to the yield locus test). The shear stress acting between bulk solid specimen and wall material can be measured. It is usual to measure wall friction at incrementally decreasing wall normal stresses. Thus, one begins with the greatest wall normal stress, σ_{w1}. At the beginning of the shear process the wall shear stress, τ_w, increases. With time, the increase of the wall shear stress becomes less until finally a constant wall shear stress, τ_{w1}, is attained (steady-state shear stress). The constant wall shear stress, τ_{w1}, is characteristic for the applied wall normal stress, σ_{w1}. After the steady-state condition is attained, the normal load is reduced. With each decrease in wall normal stress, wall shear stress, τ_w, also decreases. After a certain time, a steady-state shear stress is again attained. In this way values of steady-state wall friction at several wall normal stresses are measured. The pair of values of wall normal stress and constant wall shear stress (σ_w, τ_w) describes the kinematic wall friction at the wall normal stress, σ_w, and is used for the evaluation of the test. All pairs of values of wall normal

stress and steady-state wall shear stress are plotted in a σ_w, τ_w-diagram. The curve (or line) running through the measured points is called the wall yield locus.

The wall yield locus is a yield limit like the yield locus. The wall yield locus describes the wall shear stress, τ_w, necessary to shift a bulk solid continuously across a wall surface under a certain wall normal stress, σ_w. Since the wall yield locus is based on the shear stresses measured at steady-state conditions, it describes the kinematic friction of the bulk solid. Thus, the wall yield locus could more exactly be called a kinematic wall yield locus. To quantify wall friction, the wall friction angle, φ_x, or the coefficient of wall friction, μ, are used. The larger the wall friction angle or coefficient of wall friction, the greater is wall friction. The coefficient of wall friction, μ, is the ratio of wall shear stress, τ_w, to wall normal stress, σ_w. The wall friction angle, φx, is the slope of a line running through the origin of the σ_w, τ_w-diagram and a point of the wall yield locus. If the wall yield locus is a straight line running through the origin (Figure 1.9), the ratio of wall shear stress, τ_w, to wall normal stress, σ_w, has the same value for each point of the wall yield locus. Thus, one can obtain the identical wall friction coefficient, μ, and the identical wall friction angle, φ_x, for each point of the wall yield locus. In this case wall friction is independent of wall normal stress. The wall yield locus shown in Figure 1.9 is curved and does not run through the origin. In this case one finds a different wall friction coefficient and wall friction angle for each point of the wall yield locus. Thus, the wall friction coefficient and the wall friction angle are dependent on wall normal stress, σ_w. This can be seen by the wall friction angles, φ_{x1} and φ_{x2}, which follow for the wall normal stresses, σ_{w1} and σ_{w2}. A wall yield locus intersecting the τ-axis at $\tau_{ad} > 0$ is typical for materials tending to adhere at walls (e.g. like moist clay). The shear stress, τ_{ad}, at the point of intersection is called adhesion.

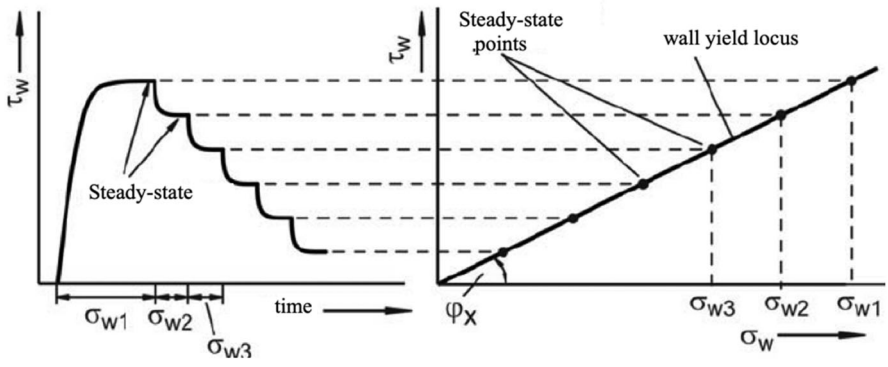


Fig.1.9 Course of wall shear stress in a wall friction test; wall yield locus.

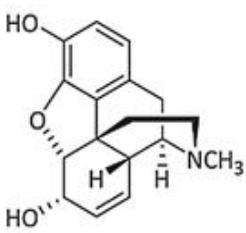
Wall friction can be measured with the shear testers. The bottom ring of the shear cell is replaced by a sample of wall material (e.g. stainless steel, coated steel). The wall normal stress is then adjusted by the normal force, F_N, and the shear force, F_S, is measured following the procedure outlined above.

The setup of the wall friction shear cell of the Schulze ring shear tester. The annular bottom ring contains the sample of the wall material. On the top of the wall material sample is the bulk solid specimen, which is covered with the annular lid of the shear cell. The lid is connected to the crossbeam. Except for the geometry of bottom ring and lid, the setup is similar to the setup of the shear cell for flow properties testing. To measure wall friction the shear cell is rotated slowly in the direction of arrow ω, while the lid is prevented from rotating by the two tie rods. The forces acting on the tie rods, F_1 and F_2, are measured. The layer of bulk solid located between the lid and the surface of the wall material sample is prevented from rotating by the lid, which has a rough underside. Thus, the bulk solid is shifted across the surface of the wall material sample while it is subjected to the normal stress, σ_w. The wall shear stress, τw, is calculated from the F_1 and F_2.

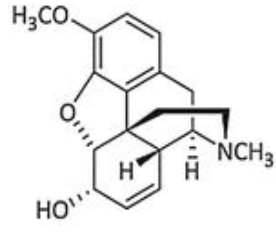
STRUCTURE MODIFICATION

During the design of all mechanical structures, it is necessary to fulfil certain mechanical criteria. Any modification made onto a structure has an effect of changing the structural properties, such as, resonant frequencies, mode shapes and deformation distribution. When an aircraft is modified by attaching external payload to it, the dynamic behaviour of the aircraft changes. This change can be critical as it may cause serious vibration problems; hence, dynamic behaviour of the modified aircraft has to be predicted in the design stage. Molecular modification by nature has been going on since the beginning of life on this planet. In the relatively short time since chemistry has developed into a science, the chemists had learned well from nature the significance of small changes in chemical structures of drugs to the biological activity in living organisms. For example, opium, the sun-dried latex of the unripe fruit of *Papaver somniferum*, cultivated from early times for this drug, contains at least 23 alkaloids. Of the major alkaloids three—morphine, codeine, and thebaine—contain the morphinan ring system. Morphine for more than a century has been the most important agent for the relief of pain. Codeine, with its phenolic hydroxyl group protected by methyl, has about one tenth the analgesic activity of morphine. But as such has found its place in the relief of mild pain and as an antitussive agent. Thebaine differs from codeine by the addition of methylene groups and the removal of two hydrogen atoms, is neither an analgesic nor an antitussive. Instead, it resembles strychnine and brucine in its spinal convulsant properties. It is not used in medicine; it has utility, however, in the synthesis of codeinone derivatives, some of which are useful as analgesics. The chemist has identified the morphine-analgesic

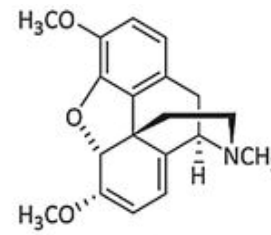
pattern and has gone far beyond nature in his quest for an analgesic with the power of morphine but without its liabilities.



morphine



codeine



thebaine

The chemical structure affects the physicochemical properties of a molecule which in turn affects its drug-like properties. In a structural modification problem, the additional dynamic stiffness matrix due to structural modification is given by

$$[\Delta A] = [D] - [D_0] \quad \text{.....(1.1)}$$

Where, [D] and [D_0] are the dynamic stiffness matrices of the modified and original structures, respectively. For lumped modifications [ΔD] corresponds directly to dynamic stiffness matrix of the modifying structure. For distributed modifications, it is calculated by using Eq. (1) which may not correspond to the dynamic stiffness matrix of the modifying structure. When the size of the bounded region which covers the modifying area is larger, the error introduced to [ΔD] will be smaller. In order to avoid such errors, a different approach for the application of the structural modification technique is used. If distributed modification is applied to an original structure in such a way that additional (degree of freedom) DOF is introduced, then it is not necessary to use Eq. (1) to calculate the additional dynamic stiffness matrix due to structural modification, as the problem will be a structural coupling problem. In that case, the additional dynamic stiffness matrix due to structural modification will be equal to the dynamic stiffness matrix of the modifying structure which can directly be used in the structural modification method.

Fig.1.10 Original beam.

Fig.1.11 Modified beam.

For example, the dynamic stiffness matrices of the original and modifying structures for the modified beam in Figure 1.10 are given by

$$[D_0] = [K_0] - \omega^2[M_0] + i[H_0]$$

$$[D_{mod}] = [K_{mod}] - \omega^2[M_{mod}] + i[H_{mod}]$$

Where, $[K_0]$, $[M_0]$ and $[H_0]$ are the stiffness mass and structural damping matrices of the original structure,

$[K_{mod}]$, $[M_{mod}]$ and $[H_{mod}]$ are stiffness, mass and structural damping matrices of the structure

They all can be obtained directly from the (Finite Element model) FE models of the original and modifying beams. When additional DOF is introduced to the original structure, the dynamic stiffness matrix of the modified structure can be obtained by assembling the dynamic stiffness matrices of the original and modifying structures. Similarly, for distributed modifications, if additional DOF is introduced to the original structure, there is no need to use Eq. (1); instead, additional dynamic stiffness matrix due to structural modification can directly be obtained.

Historically, natural substances had been used as the main sources of medicine to treat a wide spectrum of human diseases. Although the total number of new chemical entities launched has declined in recent years, structurally diverse natural products (NPs) continue to be used as leads or main sources for novel drug discovery. Among the 112 drugs have been approved by the Food and Drug Administration (FDA) between 1999 and 2013, out of which 31 drugs (28%) were developed based on natural pharmacophores. Although NPs have a proven track record in drug discovery and uncontested unique structural diversity, there are still several problems associated with NPs. Typical restrictions for the development of novel drugs from NPs include their,

* Low solubility,
* Metabolic instability, and
* Unknown exact mechanisms of action,

which especially hamper the development of similar drugs. Additionally, many NPs are often structurally complex, and their 'heavy 'structures break Lipinski's rules and most likely will limit their absorption from the gut into the blood, thus impeding oral formulation[54]. Furthermore, the intellectual property situation is often ambiguous for unmodified NPs. Therefore, it is highly desirable to develop NPs through structural modification to achieve the final candidate drug. Many NPs and synthetically modified natural product derivatives have been successfully developed for clinical application to treat human diseases in almost all therapeutic areas. These involved well-known drugs such as penicillin (antibacterial), morphine (analgesic), artemisinin (antimalarial), paclitaxel (anticancer), etc. These efforts demonstrate that, despite many limitations of NPs, with reasonable modifications, sometimes even alteration of a single atom, may result in the discovery of a novel drug. For example, a change in the logP of NPs may increase their potency and efficacy against drug resistance cells. Removing unnecessary groups of NPs

can truncate them to be analogues with more simple structure. On the other hand, introduction of water-soluble groups would help to improve the water solubility of NPs.

- NPs are vital sources of drug discovery; their various deficiencies or shortcomings limit their wide applications in drug development, and thus, structural modification of NPs is in urgent necessity to develop the novel entities with specific properties.
- Major changes may be required for the structural modification of NPs, but commonly they require fine tuning. In somecases, a single alteration can make a great difference.
- NPs embody inherent structural complexity and biological activity, and modification of NPs is a versatile approach to explore their mode of actions.
- Making logical and systematic changes to NPs is an effective way to increase their potency and activity spectrum and therefore counter resistance mechanisms.
- Biologically active NPs often have privileged scaffolds and diverse biological activities; sometimes, with proper modifications, they could be used for new treatments.
- Complex NPs often suffer from high molecular weights and poor oral bioavailability. Structural modification may provide structurally simpler compounds that retain bio-activities.
- Structural modifications that reduce the compound's binding affinity or reactivity at the labile site may increase metabolic stability.
- Low aqueous solubility is a common problem in developing NPs into drugs, but chemical modification is a powerful strategy that could be applied to enhance the water solubility of NPs.
- Because of their unique chemical properties and potential interactions with disease-associated proteins, natural products will remain a reliable source of lead compounds in drug discovery.

DRUG-EXCIPIENT COMPATIBILITY STUDIES

Drug-excipient incompatibility means that the drug is inactivated through either decomposition or loss of drug by its conversion to a drug-loss by its conversion to a less favourable physical or chemical form. It can affect the safety, therapeutic efficacy, appearance or elegance. When two or more drugs and/or excipients are mixed and if they are antagonistic and affect adversely the safety, therapeutic efficacy, appearance or elegance then they are called incompatible.

Importance of drug-excipient incompatibility study

Stability of a dosage form can be maximised. Any change in physical or chemical interaction between drug and excipient can affect the bioavailability of the drug. It can help to avoid the surprise problems. If the drug-excipient incompatibility test is performed, the possible reaction before formulating the final dosage form can be known. Drug discovery can bring only new chemical entity. After formulation and processing with suitable excipients, it becomes the drug product. With the help of drug-excipient compatibility study, suitable type of excipients can be selected. Drug-excipient compatibility study data is necessary for submission of investigational new drug to drug regulatory agency. Now it has become compulsory to submit these data to get approval of USFDA for any new formulation. To prepare a list of excipients that can be used to formulate any dosage forms, one would not consider using sucrose or lactose. If the drug substance under consideration is a primary amine. This system has the scope for interaction to form a coloured compound, this can be readily detected by a change in colour.

Types of incompatibility

There are three types of incompatibility between drug and excipient, such as:

1. ***Physical incompatibility:*** It involves the change in the physical state of the formulation, which means the change in colour, liquefaction, phase separation or immiscibility.
2. ***Chemical incompatibility:*** It involves undesirable change in formulation which is due to formation of new chemical compound with undesirable activity or our formulation undergoes hydrolysis, oxidation, reduction, precipitation, decarboxylation, racemizatoon.
3. ***Therapeutic incompatibility:*** It is one type of *in vivo* compatibility. This involves change in therapeutic response of the formulation which is undesirable to patient as well as physician.

Reasons for compatibility study

1. Identification of compatible excipients for a formulation.
2. Identification of stable storage conditions for drug in solid or liquid state.

Solid state reaction

Solid state reactions are much slower and more difficult to be interpreted than solution state reactions. Because there are reduced number of molecular contacts between the drug and excipient molecules and multiple phase reactions occur. Preformulation is the first step in the rational formulation of drug substance (API). It is an investigation on the physicochemical properties of the drug substance alone and also in combination with excipients. Investigation of the possible incompatibilities between the drug and various excipients is an important part of the preformulation. Sometimes, the

formulation of a drug substance involves it after blending with different excipients to manufacture easily and administer the dose of a drug effectively. Excipients are known to

* Facilitate the administration, and
* Modulate the release of the active component, drug.

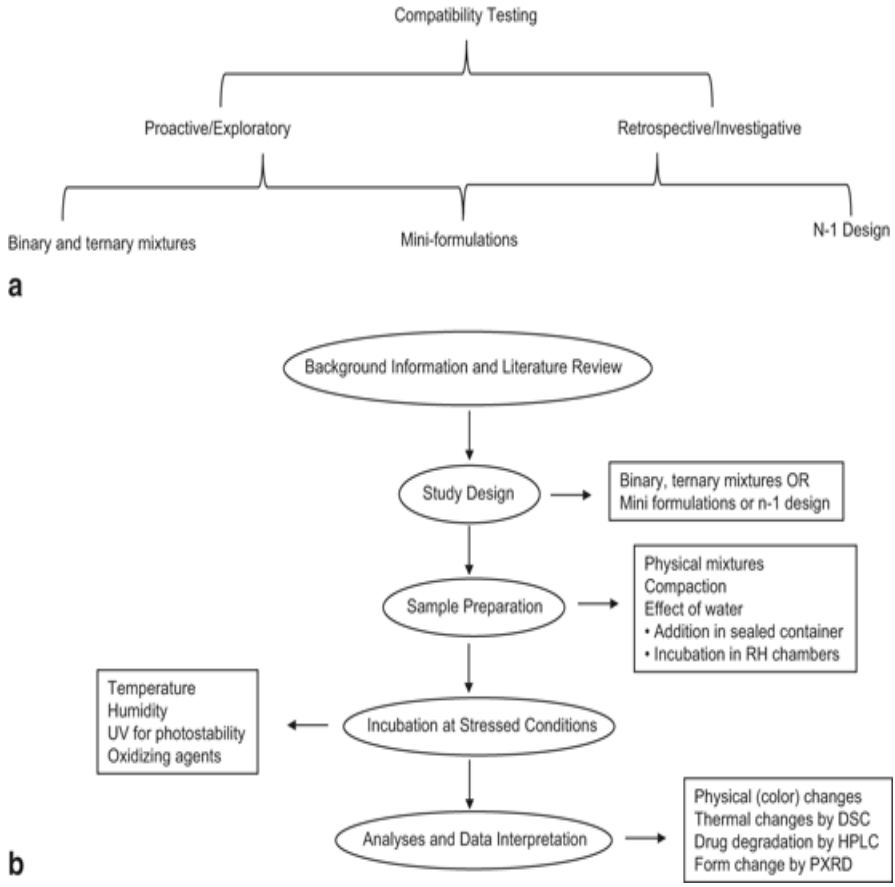
The excipients are used to stabilise the drug-product against degradation from the environment.

* Most of the excipients do not have any pharmacological action.
* They are used to exert some useful properties to the formulation.
* They can also give rise to inadvertent and/or unintended effects such as an increased degradation of the drug.

The physical and chemical interactions between the drugs and excipients can affect the chemical nature, the stability and bioavailability of the drug products, consequently their therapeutic efficacy and safety. Thus, the drug-excipient compatibility study plays an important role in identifying the possible duration of interaction between the excipients used in the formulation and the drug concerned. Commonly, for detection of physical-chemical investigation and detecting the possible interaction, the thermal analysis such as DSC, DTA, DTG, ITC, spectroscopic methods such as FT-IR, X-ray diffraction, NMR, and chromatographic methods such as LC, LC-MS/MS, dissolution tests etc., are performed. The most sensitive and appropriate methods for detection of possible interaction is thermal analysis. However, the method can be unspecific, and the results are difficult to interpret. Sometimes, the results are found to be false positive or false negative, and thus, difficult to be interpreted.

Differential Scanning Colorimetry (DSC) has been currently used in this area. The major advantage of DSC is its ability to quickly screen the potential excipients for incompatibilities derived from the appearance, shifts or disappearance of peaks and/or variations in the corresponding ΔH (enthalpy of transition). Other characteristics of this method is that the sample required is low. Although DSC is a valuable technique, the interpretation of the data is not straightforward. In this method, the sample is exposed to high temperature, up to 300°C or more. This high temperature is not experienced by the dosage form. Therefore, DSC results should be interpreted very carefully.

From this point of view, the IR spectroscopic methods are relatively less sensitive. This method is complementary for the thermal-analytical techniques, particularly due to detection of the atom groups involved in the excipient/API interaction and these allow the quantitative estimation of these interactions. The aim of study was to analyse by DSC and IR studies the compatibility of some excipients with potential use in binary or ternary mixtures, as vehicles for the preparation of mucoadhesive systems with antimicrobial (MZ, CD) or anti-inflammatory drug substances (IB).



METHODS OF DETERMINATION OF DRUG-EXCIPIENT COMPATIBILITY

The drug-excipient compatibility studies are carried out for the purpose of identifying, quantifying and prediction of potential interactions (physical or chemical). Moreover, these impact of these interactions on the manufacturability, quality and performance of the final drug product. On the basis of previous knowledge about the physico-chemical properties and about the degradation mechanisms of the drugs and the excipients, these studies are finalised. In addition to evaluation of the direct interactions between the API and the excipients, the influence of factors such as water (moisture) and temperature is also explored in these studies. These factors are known to accelerate the possibility, and the extent of drug-excipient interactions either by altering the physico-chemical properties or rate of degradation of the drugs and/or excipients. These studies generally involve bringing the API and the excipient/s into intimate contact with each either as physical admixtures in a predetermined ratio, or as a preliminary dosage form; and subjecting them to

various stress conditions. The physico-chemical and performance attributes of the API and the excipients are then evaluated using one or more analytical techniques.

The evaluation of drug-excipient compatibility includes a broad range of thermal and non-thermal analytical techniques. These techniques are diverse with respect to their-

* Principles of operation,
* Sample size,
* Duration of analysis,
* The type of stress i.e. thermal, mechanical etc.

Moreover, due to the wide variation in the chemical and physical nature of drugs and the excipients, and the complex nature of their interactions, there is a lack of universal standards in the methodology used in the evaluation of compatibility between the API and the excipients.

There has been a significant increase in the number of individual studies reporting the use of one or more methods for screening the API-excipient compatibility. The commonly reported methods include, thermo-analytical techniques such as differential scanning calorimetry (DSC), thermo-gravimetric analysis (TGA), differential thermal analysis (DTA), isothermal microcalorimetry (ITC), hot stage microscopy and non-thermal techniques such as x-ray diffraction (XRD), fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), high performance liquid chromatography (HPLC), near infrared spectroscopy (NIR) and solid state nuclear magnetic resonance spectroscopy (ssNMR)[55]. Applications of these techniques as drug-excipient compatibility screening tools, along with their advantages and drawbacks are briefly discussed below.

Thermal techniques

Differential scanning calorimetry

Differential scanning calorimetry (DSC) is the most common thermal technique used for testing the excipient incompatibilities. This technique usually requires a small size of sample, and the results are obtained relatively rapidly. The thermogravimetry/derivative thermogravimetry (TG/DTG) and DSC techniques are used to evaluate the compatibility between ketoprofen and several excipients including corn starch, microcrystalline cellulose, colloidal silicon dioxide, lactose, PVP K30, magnesium stearate and talcum. The results of the study demonstrated that DSC helps us to ascertain any incompatibilities in the formulation components. These may include the changes in appearance, in endothermic or exothermic peaks, or in enthalpy curves. In a similar study, it has been evaluated the compatibility of the acetylsalicylic acid, a non-steroidal anti-inflammatory drug, with

pharmaceutical excipients of common use such as diluents, binders, disintegrants, lubricants and solubilising agents. The results confirmed the utility of DSC as a sensitive and a specific technique in assessing the drug-excipient compatibility. Although DSC is frequently used due to its inexpensive and eco-friendly nature, it is important to understand that it may not provide accurate results in every situation. For example, amorphous API are known to reduce the enthalpy of fusion of the API. DSC often involves exposing the formulations to temperatures that may degrade excipients (as high as 300°C) and are physiologically unrealistic. As a result, DSC may sometimes be misleading and is often used in combinations with other techniques to ensure accuracy. This technique, however, can be used in combination with SEM to search for physical incompatibilities within a formulation.

Thermogravimetric analysis

Thermal testing improves the thermogravimetric analysis (TGA). This test, and the DSC, examines the mass of formulation lost as a percentage with increasing temperature. Additionally, thermogravimetry and derivative thermogravimetry can determine the reactivity of each excipient with the API or with each other. The TGA is used, in addition to the DSC to check the compatibility of acetylsalicylic acid with 11 other excipients. The thermogravimetric analysis, derivative of thermogravimetric analysis, and DSC revealed that all excipients, aside from polyvinyl pyrrolidone (PVP) and magnesium stearate, have been compatible with acetylsalicylic acid. In another study, the compatibility of ketoprofen with similar, commonly used excipients using DSC, TGA, DTGA, PXRD and FTIR is assessed. The TGA results along with other techniques revealed a possible interaction between the ketoprofen and PVP K30, and between ketoprofen and magnesium stearate. In a study on the compatibilities between excipients and sildenafil citrate has been conducted, the DSC and TG curves showed that after heating to a range of 190 - 229.5^{o}C, 28.8% of citric acid was evaporated. What remained was the sildenafil base that later decomposed at higher temperatures. The TG curves in this analysis helped to understand each temperature range at which excipients would be lost.

Isothermal microcalorimetry

Isothermal microcalorimetry (IMC), or isothermal stress testing, is another method that helps the determination of the integrity of the pharmaceutical formulations. The test involves storing the excipients for three to four weeks, with or without moisture, at temperatures above 50^{o}C. This process simulates drug ageing and stimulates excipient interactions. The test has the capacity to determine compatibilities but is limited by its time-consuming and arduous nature. After a predetermined storage period, the contents of the formulation are analysed using methods such as HPLC and DSC. IMC is used in

combination with DSC to understand the compatibilities between promethazine HCl and lactose monohydrate, and zinc stearate. It has been found that after three months of storage of IMC, at accelerated stability conditions, the tablet formulation had an acceptable level of reactivity and was thermally stable. This test not only helped with determining incompatibilities, but also offset the misleading results commonly associated with DSC.

Hot stage microscopy

Methods involving microscopy are used to study the drug formulation morphology and to identify any physical incompatibilities associated with the excipients. A study has been conducted to evaluate the compatibility of ibuproxam and excipients using DSC. Hot-stage microscopy (HSM) has been used as an adjunct to DSC. The process required only a small amount of sample, and the microscopy results confirmed that the incompatibilities found in the DSC analysis was due in part by the dissolution of excipient at an elevated temperature. In a different study, conducted by Aigner et al, HSM has been used to find the thermal behaviour of aceclofenac[56]. DSC revealed one sharp endothermic peak at 153.1ºC. Magnesium Stearate, an excipient used in this formulation, showed three endothermic peaks on the DSC analysis at 89.2ºC, 104.5ºC, and 203.5ºC. The HSM analysis showed that the magnesium stearate melted first and subsequently dissolved the aceclofenac. HSM thus essentially explained the disappearance of aceclofenac and the peak associated with magnesium stearate on the DSC. It is thus advisable that when developing formulations, both DSC and HSM be used in conjunction to ensure accuracy and compatibility of drug excipients.

Non-thermal Techniques

Infrared, near Infrared and Raman Spectroscopy

Infrared (IR), near-infrared (NIR) and Raman spectroscopy are the most commonly used non-thermal techniques for the screening of drug-excipient compatibility. These techniques provide a unique fingerprint to the API and the excipients based on their physical and chemical properties. Due to the highly sensitive nature of these techniques, any little deviations in the physico-chemical properties of the API as a result of the interactions with the excipients are readily detected. Commonly observed physico-chemical changes due to drug-excipient interactions include polymorph transitions, dehydration, formation of hydrates/solvates, changes in the deformation behaviour of powders etc. Some of the common advantages of these techniques include rapid analysis, quick and easy detection of incompatibilities due to spectral shifts and the detection of interaction by-products. The compatibility of aceclofenac with various tableting excipients such as Carbopol 940, hydroxypropyl methylcellulose, microcrystalline cellulose, Aerosil 200 and magnesium stearate were

investigated by Aigner et al. using DSC and FT-IR. The study results showed the occurrence of interaction between aceclofenac and magnesium stearate resulting in the formation of magnesium salt of aceclofenac. The other excipients were found to be compatible with the drug i.e. no significant interaction was observed between aceclofenac and other excipients studied. Similarly, Pani et al. assessed the compatibility of nateglinide with various excipients in the development of immediate release tablets of nateglinide using DSC, IR and IST. The IR results revealed the absence of any significant incompatibilities between the API and the tested excipients. Blanco et al. evaluated the polymorphic transition in Dexketoprofen Trometamol (DKP) production samples obtained by direct compression and wet granulation using Multivariate Curve Resolution - Alternating Least Squares (MCR–ALS) methodology to obtain the NIR spectra for samples without pretreatment. The results showed that significant polymorphic transition occurred in DKP during wet granulation; whereas no changes were observed with samples processed via direct compression. Dave et al. investigated the influence of plasticiser (triethyl citrate, TEC) level on the breaking force of extended-release matrix tablets prepared by roller-compaction. The multivariate analysis of the results demonstrated the feasibility of NIR spectroscopy in evaluating the influence of TEC levels on the breaking force of prepared tablets. Kogermann et al. explored the dehydration of piroxicam monohydrate in compacts using terahertz pulsed spectroscopy (TPS), Raman spectroscopy, and reflectance near-infrared (NIR) spectroscopy[57]. The study results concluded that the Raman and NIR spectroscopy were suitable for monitoring the loss of moisture along with the structural changes that occurred during the dehydration of samples.

Powder X-ray Diffraction

In the preformulation stage of the drug development process, powder x-ray diffraction (PXRD) is used to characterise the crystalline nature of materials. PXRD is a widely used polymorph screening technique for the API. Each crystalline material exhibits a unique x-ray diffraction pattern, as displayed by the peak intensities against a range of diffraction angles (2θ). Any interactions between the API and excipients that results in a change in the crystalline form of the API is generally exhibited as a shift, appearance or disappearance of these peak intensities. Thus, PXRD analysis can provide useful information regarding the influence of drug-excipient interactions on the polymorphic changes in the API. PXRD analysis may also be useful in the evaluation of API polymorphic transitions occurring as under the influence of moisture and temperature changes during processing, albeit only in the absence of interference from any excipient peaks. Tita et al. assessed the compatibility between ketoprofen and several excipients such as corn starch, microcrystalline cellulose, colloidal silicon dioxide, lactose, polyvinyl pyrrolidone K30, magnesium stearate and talc using DSC, TGA, FTIR and

PXRD. The PXRD data confirmed the DSC and TGA results indicating a possible interaction between the KT with polyvinyl pyrrolidone K30 and magnesium stearate, as demonstrated by the changes in the intensity of peaks as well as disappearance of certain peaks observed in the spectra of individual components. In a similar study, Tita et al. evaluated the compatibility of the acetylsalicylic acid (ASA) with pharmaceutical excipients including diluents, binders, disintegrants, lubricants and solubilising agents using DSC, TGA, FTIR and PXRD. The x-ray analysis results confirmed a possible chemical interaction between the ASA with polyvinyl pyrrolidone K30 and magnesium stearate, and a possible physical interaction with colloidal silicon dioxide and stearic acid. In another study, Roumelli et al. demonstrated the compatibility of trandalopril with α-lactose monohydrate, microcrystalline cellulose, and pre-gelatinised starch using PXRD analysis of the physical mixtures of the drug with the selected excipients.

Solid-state Nuclear Magnetic Resonance Spectroscopy

Solid-state nuclear magnetic resonance (ssNMR) spectroscopy has emerged as a common analytical tool for the analysis of drug-excipient interactions in recent years. This technique identifies the interactions between the API and the excipients through variations in the chemical shift occurring as a result of change in the electron density around the interaction sites. Some of the known advantages of this technique include higher selectivity, limited interference from excipients and the ability to detect polymorphic transitions in the API. In addition, the presence and influence of water on the drug-excipient interactions are easily detected by this method. The main drawback of this technique is the duration of analysis, which often can be lengthy and complex. Chen et al. investigated the acid–base reactions of solid materials, a common type of drug–excipient interaction using binary mixtures (1:1) of pure α-form indomethacin and sodium bicarbonate as model drug and excipient respectively. The ssNMR results, along with those obtained from PXRD analysis confirmed the transformation of the mixtures into the micro-crystals of sodium indomethacin trihydrate, indicating the presence of drug-excipient interaction. In another study, Skotnicki et al. evaluated the compatibility of bisoprolol fumarate with amorphous valsartan using DSC, TMDSC, ssNMR and PXRD. The study results indicated a strong interaction between bisoprolol fumarate and valsartan above 60°C[58]. The ssNMR data provided the information on the incompatibility at a molecular level. Schachter et al. characterised the nature of interaction between ketoprofen and polyethylene oxide (PEO) in a solid dispersion formulation using ssNMR along with other analytical techniques. The 13C single pulse/magic angle spinning NMR indicated the presence of hydrogen bonds between the carboxylic group of ketoprofen and the ether oxygen of PEO, indicating a drug-excipient interaction.

Microscopic Techniques

Scanning Electron Microscopy

The interactions between the API and the excipients often result in polymorphic transitions and changes in crystal habits of the API. Scanning electron microscopy (SEM) provides useful information on such changes by characterizing the surface morphology of pharmaceutical APIs. Although SEM may not independently provide information on the nature of drug-excipient interaction at a molecular level for example, chemical and thermal transitions; combining SEM with other analytical techniques such as DSC/TGA, HSM, and other thermal techniques can significantly benefit to the overall characterisation of the incompatibilities. Mura et al. assessed the compatibility of ibuproxam with commonly used excipients such as corn starch, Avicel, sodium carboxymethyl cellulose, polyethylene glycol 4000 (PEG-4000), palmitic acid, stearic acid, Ca- and Mg-stearate, polyvinyl poly-pyrrolidone (PVPP) and polyvinyl pyrrolidone K30 (PVP K30). The results obtained from the SEM analysis were in general, in agreement with and confirmatory to those obtained from DSC and HSM.

Chromatographic Techniques

High Performance Liquid Chromatography

High performance liquid chromatography (HPLC) is the most widely used analytical technique for determining the API content in a formulation. This technique can be very useful in situations where the drug-excipient interaction may lead to a quantitative change in the API. In drug-excipient compatibility studies, the formulations or the drug-excipient mixtures are subjected to high temperatures for a predetermined period of time i.e. isothermal stress testing (IST) to accelerate any chemical incompatibilities. This is followed by determination of drug content using HPLC analysis, thus identifying any quantitative loss of drug as a result of interactions with the excipients. Gu et al. screened the compatibility of moexipril HCl, an angiotensin-converting enzyme (ACE) inhibitor, with commonly used filters, disintegrants, lubricants, glidants, and coating agents using IST along with HPLC. The HPLC results confirmed the presence of interactions between the drug and the excipient. The results also indicated that neutralization of the acidic drug by the basic excipients suppressed drug degradation. In another study, Julio et al. evaluated the compatibility of sildenafil citrate with colloidal silicon dioxide, cross-carmellose sodium, lactose, mannitol and sucrose using DSC, HSM and HPLC. The accelerated stability studies results showed the presence of incompatibilities between the drug and the selected excipients. However, it was also observed that some incompatibilities detected by HPLC, were not detected by DSC and vice-versa. The study demonstrated the benefits of complementing the thermal techniques with HPLC in detecting incompatibilities and providing more robust and accurate approaches for pre-

formulation studies. Along with the commonly recognised advantages of HPLC such as accuracy and robustness, the main drawback of the technique is that this technique is time consuming and complex. To evaluate the drug-excipient compatibility, this is a very useful supportive tool in preformulation studies.

Liquid State Incompatibility Reaction

The reactions occur in the liquid state are easier to detect as compared to solid state reactions. For detection of unknown reactions responsible for incompatibility of two liquids, the program set up is similar to as in case of solid dosage forms. According to the stability guidelines decided by FDA, following conditions are to be evaluated in solution/ suspension preparations of the bulk drug substances:

Acidic or alkaline pH

Presence of added substances, such as, chelating agents, stabilisers, etc.

Effect of stress testing conditions…….

High Oxygen and Nitrogen atmospheres.

Procedures to be followed are:

Place the drug in solution of additives,

Both flint and amber vials are used,

In many cases, autoclaved samples are examined. This will provide following information:

Susceptibility to oxygen,

Susceptibility to light (exposed),

Susceptibility to heavy metals

In case of oral liquids, compatibility with ethanol, glycerin, sucrose, preservatives, buffering agents, colouring agents, flavouring agents etc. are carried out.

Exercise

Multiple Choice Questions

1. The physical or chemical stability and the morphology of the drug product depend mainly on …….
   a) The selection of an appropriate polymorph,
   b) Appropriate granulation method
   c) The selection of an appropriate cocrystal of excipient
   d) None of the above
2. The pharmaceutical industry is developing new molecules with different modalities, such as, ……..
   a) Macrocycles, b) Peptides,
   c) All of the above d) None of the above
3. Co-processed API can be defined as *a* drug substance, manufactured in a drug manufacturing facility, that contains the API in addition to one or more covalently bonded……
   a) Active component
   b) Non-active component,
   c) Binder
   d) Disintegrant
4. When equilibrium attains between a crystalline phase and its surroundings, the statistical amount of growth units exchanged between the two phases is ……
   a) Sometimes not same
   b) Sometimes same
   c) Not same and change with time
   d) The same and does not change with time.
5. When equilibrium attains between a crystalline phase and its surroundings, the statistical amount of growth units exchanged between the two phases remains …….
   a) Same and does not change with time.
   b) Different and that changes with time.
   c) Same but changes with time.
   d) None of the above

6. Which of the following statement is correct?
   a) The crystal structure, on which the surface structures (i.e., the profiles) of the faces depend, these crystal defects are caused by external factors.
   b) The supersaturation, nature of solvent, solution composition, impurities, physical conditions (temperature, solution flow, electric and magnetic field, microgravity, ultrasound, etc.) are the internal factors.
   c) The supersaturation, nature of solvent, solution composition, impurities, physical conditions (temperature, solution flow, electric and magnetic field, microgravity, ultrasound, etc.) are the external factors.
   d) The supersaturation, nature of solvent, solution composition, impurities, physical conditions (temperature, solution flow, electric and magnetic field, microgravity, ultrasound, etc.) are the mixed factors.
7. Kinetic roughening of the crystals occurs……
   a) Above the roughening temperature when supersaturation exceeds the d critical value.
   b) Below the roughening temperature when supersaturation does not exceed the critical value
   c) Above the roughening temperature when supersaturation does not exceed the critical value.
   d) Below the roughening temperature when supersaturation exceeds the critical value
8. The flow properties of solid depend on several parameters, such as……..
   a) Particle size distribution,
   b) Moisture
   c) All of the above
   d) None of the above
9. For shear to failure the normal stress acting on the specimen is decreased to a value σ_{sh}, which is …….
   a) More than the normal stress at pre-shear, σ_{pre}.
   b) Less than the normal stress at pre-shear, σ_{pre}.
   c) Less than the shear stress, τ,
   d) Less than the normal principal stress σ_1

10. If several yield loci are measured at different stress levels, that is, with different normal stresses at pre-shear, σ_{pre}, ……
    a) Each yield locus represents another state of consolidation and another bulk density.
    b) Each yield locus represents same state of consolidation and same bulk density.
    c) Each yield locus represents same state of consolidation and another bulk density.
    d) Each yield locus represents another state of consolidation and same bulk density.
11. When an aircraft is modified by attaching external payload to it,…….
    a) The dynamic behaviour of the aircraft does not change.
    b) The behaviour of the aircraft changes.
    c) The behaviour of the aircraft does not change.
    d) The dynamic behaviour of the aircraft changes.
12. In a structural modification problem the additional dynamic stiffness matrix due to structural modification is given by……..
    a) $[\Delta A] = [D] - [D_0]$
    b) $[D] = [\Delta A] + [D_0]$
    c) $[\Delta A] = [K_0] - [D_0]$
    d) $[\Delta A] = [D] - [H_0]$

    where, [D] and $[D_0]$ are the dynamic stiffness matrices of the modified and original structures, respectively, $[\Delta D]$ is the dynamic stiffness matrix of the modifying structure, $[K_0]$ is the stiffness mass of the original structure, and $[H_0]$ is the structural damping matrices of the original structure.
13. Making logical and systematic changes to NPs is ……..
    a) An effective way to decrease their potency and activity spectrum and therefore counter resistance mechanisms.
    b) An effective way to increase their potency and activity spectrum and therefore counter resistance mechanisms.
    c) An ineffective way to decrease their potency and activity spectrum and therefore counter resistance mechanisms.
    d) An ineffective way to increase their potency and activity spectrum and therefore counter resistance mechanisms.
14. Drug-excipient incompatibility can affect ……
    a) The safety, and therapeutic effect.

b) The safety, and appearance.
c) The therapeutic efficacy, appearance, or elegance
d) The safety, therapeutic efficacy, appearance, or elegance

15. The techniques for evaluation of drug-excipient compatibility are diverse with respect to their…
    a) The type of stress,
    b) Duration of analysis,
    c) All of the above
    d) None of the above
16. The commonly reported methods include thermo-analytical techniques such as……..
    a) Differential scanning calorimetry, isothermal microcalorimetry,
    b) Thermogravimetric analysis, differential thermal analysis, hot stage microscopy
    c) All the above
    d) None of the above
17. Which of the following states DSC?
    a) Differential scanning calorimetry
    b) Differential scanning colorimetry
    c) Diffusional scanning calorimetry
    d) Diffusional scanning colorimetry
18. IMC stands for……
    a) Internal Microcalorimetry
    b) Isothermal Microcalorimetry
    c) Isothermal Micro colorimetry
    d) Industrial Microcalorimetry
19. Mark the following statement true or false
    a) Methods involving microscopy are used to study the drug formulation morphology and to identify any physical incompatibilities associated with the excipients.
    b) True
    c) False
20. Mark the following statement true or false
    a) The drug-excipient compatibility studies are carried out for the purpose of identifying, quantifying and prediction of potential interactions (physical or chemical).
    b) False
    c) True

Short Questions

1. What is molecular optimization? Write down the commercial applications of co-processing of APIs.
2. What is crystal habit? What are the factors that can influence the crystal habit?
3. Write down the procedures used to study the change in crystal habit.
4. Explain the uniaxial compression test.
5. What is meant by Time consolidation (caking)?
6. What is the importance of drug-excipient compatibility study?
7. Name the methods used for study of drug-excipient incompatibility study.
8. Discuss the thermogravimetric analysis.
9. Discuss the isothermal microcalorimetry.
10. Write a note on hot state microscopy.

Long Questions

1. What is meant by the term molecular optimization, write in brief.
2. Write down in short, the various aspects of crystal morphology.
3. What do you know about polar crystals and kinetic roughening?
4. Describe the flow properties of a powder or a bulk solid.
5. How does introduction of water-soluble groups would help to improve the water solubility of NPs.?
6. Explain the term, 'solid state reaction'.
7. Describe the methods of isothermal calorimetry and hot stage microscopy.
8. What are the non-thermal methods used for drug-excipient incompatibility test. Discuss the method of scanning electron microscopy.
9. What is chromagraphic method such as High performance liquid chromatography?
10. What do you know about Solid-state nuclear magnetic resonance spectroscopy? What for this method is used?

Answers

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
a	c	b	d	a	c	d	c	b	a	d	a	b	d	c	d	a	b	b	c

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