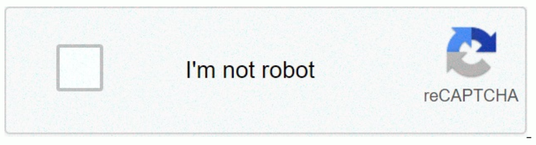

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Drug excipient compatibility study guidelines

Ajit S. Narang, ... Krishnaswamy S. Raghavan, in developing solid oral dosage forms, 2009Excipient compatibility studies are carried out with the primary purpose of selecting dosage form components that are compatible with the drug. Methodically-conducted experiments also provide additional information about the stability profile of the drug, and identify degradation products and mechanisms. Moreover, if the stability of the drug is found to be lacking, strategies to mitigate the instability of the drug can be adopted. The guidelines and principles presented in this chapter will be useful in appropriate design, behavioural and interpretation of compatibility studies to help accelerate formulation development activities and prevent or reduce surprises in drug development. Kevin Coleman Bynum, in Separation Science and Technology, 2011Mania of the techniques described above, exciting compatibility, mixing uniformity through HPLC decomposition, and content uniformity/testing by HPLC can be effective automatically provided by robotic sample preparation. Each of these techniques requires that the sample be dissolved under study in an appropriate solvent and withdrawn fully from any excitement. There are a number of commercially available products that have proven to be effective and robust in this sample preparation role. This robotic process can reduce both the analyst hours required to prepare a number of samples, and reverse time on sample analysis, since the robotic systems will operate unattended over the night and on weekends. Of course, there's a cost to paying for lab automation. There is a significant capital cost, and then an ongoing maintenance cost for the continued operation of the system. It is also critical that a specialist in the house is available to care for the system, develop the methods and solve problems with the system. The cost of the system and specialist must be generated against the benefits of speed and laboratory capacity improvement realised with a successful automation implementation. Disha Mehtani, ... Rakesh K. Tekade, in Dosage Form Design Considerations, 2018As depicted in Fig. 9.7 (Scheubel, 2010), decomposition test is an essential part at every stage of the drug development process of nonclinical to postmarketing, performing essential functions such as drug selection, formulation selection, method optimization, IVC forecasting, biowaiver, quality, and figure Various applications of decommissioning testing in different phases of product development. Blue color with initial phase and orange color showing late-stage development; black color is for the market; Red arrows show interaction of decomposition and black arrows shows the interaction between the different developmental phases. Pharmaceutical product development cycle includes several stages, and at every stage decommissioning testing significant functions. Investigative New Drug Application (IND)—The application requires data from experiments done on animals and how clinical trials are planned. Decomposition testing increases lead formulation quality through salty selection such as per BCS and screens from poorly performing prototypes and saves animal resources (Guarino and Guarino, 2016). Institutional Review Board (IRB) sets up the clinical trial protocols consisting of four phases. Phase I trials test for safety. Decomposition testing performs various functions at stage 1 level, such as designing phase I formulation, salt choice of drug substance, examining excited compatibility, choosing toxicology formulations and maintaining quality standards for the first clinical drug administration. It helps identify formulations with improved decomposition properties (He et al., 2017). Phase II trials test for efficiency in addition to further safety monitoring. The final dose form to be tested in phase III studies is determined at this level. Decommissioning testing can be carried out to serve many important roles at this stage, which include process and product development, a link setting between design space and the target product profile, accompaniment to the drug emissions mechanism, regulation of the variations in drug product stability testing, and maintenance of batch release quality, as well as batch-to-batch uniformity (Blessy et al. Phase III includes joint work of the FDA and the drug's sponsor to set the phase III study protocol and determine risk-benefit data. The phase III drug development stage has the main goal of developing in-depth expertise and robust data involving the drug product and the manufacturing process for filing drug approval dossiers, to start the stability studies, and to prepare for effective and profitable product launch. Decomposition testing at this stage serves as a surrogate for in vivo bioavailability or bio-equivalence, as a tool to project the clinical performance of the drug product, and is used for process development and optimization, as well as quality control testing. Moreover, the application review is at the discreurity of the FDA under New Drug Application.Phase IV trials are carried out to analyze the outcomes developed after the drug approval and its large-scale use. Decomposition testing contributes to SUPAC or biowaiver dossier filling at this stage. Decommissioning testing also plays an important role in FDA's efforts to reduce the regulatory burden and unnecessary clinical studies in developing consistently high quality, safe and effective generic drugs without endangering the drug product quality. Agreement factor data for test drug and reference listed drugs can be used for this purpose. Wenlei Jiang, Lawrence X. Yu, in developing solid oral dosage forms, 2009Quality by design requires identification of mechanistic and formulation factors affecting drug product stability Acceptable final drug product stability cannot be accepted as evidence of excited drug drug compatibility, as end product testing only shows that the quality quality for the tested samples but do not address how the product is designed to achieve the quality. Based on ICH Q8 recommendations, a drug substance/exciting compatibility study should be evaluated as part of pharmaceutical development.40Typically, A drug dust/excited compatibility study is carried out with binary mixtures prepared in the presence/absence of added water, stored against accelerated conditions, and then analyzed by stability-charged methodology, such as HPLC.39,41 Adding water allows the pH of the drug-excited blend and the role of moisture to be examined. Alternatively, thermal analysis methods, including differential scanning calorie (DSC) and isoermic calories (ITC), are used to screen binary mixtures for their compatibility. However, data obtained via DSC/ITC is sometimes difficult to interpret or even mislead.39,42Binary mix approach is simple, but time and resource intensive, and may differ completely from a multi-component system.41 Because of these concerns, the ANDA sponsors can also conduct drug-excited compatibility studies via a prototype/trial formulation approach, with binary systems as a diagnostic In this complementary fashion can choose formulators one promising prototype formulation to move forward and identify any guilty excitement that is stability issues. The sponsor must use prior knowledge to justify inclusion or exclusion from certain excitement. For example, if the drug substance is a primary amine, and known to respond with reducing sugar, the sponsor may include it as a rationale for not having lactose tested in the excited compatibility studies. In addition, DOE can be applied in the compatibility study, to determine the chemical interactions between components. When the ANDA Q1 and Q2 are the same as the RLD, in the absence of known stability problems, historical data may be acceptable instead of compatibility studies. HOWEVER, ANDA sponsors should be warned that there may be incompatibility between drug dust and excitement used in the RLD. A systemic middle-excited compatibility study will equip the product development scientist with a mechanistic understanding of formulation factors that affect drug product stability, and reduce formulation risk, leading to a decrease in development time and cost. Jessica Cha, ... Joseph S. Ranweiler, in Separation Science and Technology, 2011The foundation of any viable stability program for a drug product begins with a thorough understanding of the chemistry of his active ingredient(s). Information about the mechanism(s) of deterioration is essential to understand how the API will behave under various environmental changes and conditions. This information is usually determined by stress degradation studies under different conditions of acidity, basicity, light, heat and execute. Other conditions can be chosen depending on the specific drug substance studies. From this stress stress knowledge of the inherent stability and mechanisms of deterioration can be obtained. The propensity of the API to preferably downgrade under specific conditions will be the area to which particular attention will need to be paid in storing and formulating the drug product, as well as choosing excitement to formulate the product. If the drug substance is prone to hydrolysis, the effect of humidity on storage will necessarily be a focal point in the stability protocol. Choosing excitement can affect the stability of the API in the formulated product. The excited compatibility studies will be discussed in Section V. The reader is referred to Chapter 3 devoted to an in-depth discussion of deterioration studies. Since the stress conditions will usually be more severe than the API will experience under its normal storage and processing conditions, the distribution and kinetics of the formation of deterioration products obtained in these studies can be extrapolated to predict the exact deterioration path(s) that would be expected at each environmental state. Identifying the degradation products at this stage is invaluable in establishing the deterioration path. Although degradation pathways under stress conditions are usually much more complex than those at room temperature, the mass distribution of the degradation products will be indicative of what deterioration products will be seen on long-term storage. The ability to separate all the degradation products will also be important for developing and validating the stability-indicating properties of any proposed analytical methods. With an understanding of the degradation chemistry, specification can be fixed that will ensure the drug substance will retain its identity, quality, purity, and strength over its expected shelf life when properly stored, which is typically up to 5 years at the marked storage condition. The ICH guideline on Stability Testing of New Drug Substance and Products1 indicates that for stress testing in respect of temperature, 10 °C increments should be studied at accelerated temperature (50, 60 °C, etc.). If applicable, the API should also be exposed to humidity conditions above 75% RH. The effect of pH on the susceptibility of the molecule to hydrolysis should be studied over a wide range, in solution or suspension. Photo stability stress test should be carried out in accordance with the conditions specified in ICH Q1B.12 Oxidative stress should always be included in any assessment of deterioration pathways. The regulatory agencies acknowledge that the synthetic scheme, specifications, testing regimen, and methods will develop after however the drug development process continues through the various clinical phases. As the database of knowledge regarding the API increases, stability data requirements also develop. In phase I, clinical studies, stability data to ensure the toxicological and proposed clinical plan. Be. stability data must be collected to demonstrate that the API remains intact during the course of the toxicological and phase I clinical trials. Depending on the stability of the API, impurities increasing during storage may be qualified by reference to these early human and animal studies. In phase II, the stability studies should support the investigative formulations used in the clinical trials to assist in choosing the final formulation, container and closure system. The information obtained from the stress studies and the phases that II studies and I have should be reflected in the protocol(s) or reported for the primary stability studies to support the final phase III clinical trials. Harry G. Brittain, in Separation Science and Technology, 2001Thermal analysis methods are defined as those techniques in which a property of the analytical is determined as a function of an externally applied temperature.48 The sample temperature is increased in a linear manner, while the property in question is continuously evaluated. This technology is used to characterize compound purity, polymorphism, buildup, deterioration and exciting compatibility.49 Thermal analysis methods are normally used to monitor endotermic processes (melting, cooking, Sublimation, evaporation, detachment, solid-solid phase transitions, and chemical degradation) as well as exoermic processes (crystallization and oxidative deposit access to this methodology are extremely useful during the conduct of preformulation studies, because carefully planned studies can be used to indicate the existence of possible mid-excited interactions in a prototype formulation. the practice of thermal analysis can be obtained from consideration of determining ordinary melting points by the study of fusion curves, for which a typical example is provided to determine this type of curve, the sample is placed within a suitable container, immersed in a bath whose temperature is increased at a fixed rate, and the temperature of the sample is monitored. As long as the fabric is a solid, it has a fixed and limited heat capacity, thus increases its temperature linear at a rate controlled by the rate of heat flow. Once the dust starts to melt, the heat capacity of the system goes intofinity because all absorbed heat is used to convert the solid phase into the liquid phase. The temperature of the sample cannot change during this process due to the infinite value of the heat capacity and the fact that any heat that enters the system only to redistdibute the relative amounts of the two phases. However, once the entire sample has melted, the heat capacity is re-fixed and restricted because the substance is now a simple liquid. Further warming leads to a linear rate of temperature rising to the next stage transition. FIGURE 6 . Fusion for melting a hypothetical compound. Differential Thermal Analysis (DTA) (DTA) an improvement to the melting point determination in that the difference in temperature between the sample and a reference is monitored as a function of temperature.50 As long as no thermal transitions occur, the temperature of the sample and the reference will be the same because the heat capabilities of the two are roughly equivalent. However, differences in temperature between the sample and referral are manifested when changes occur requiring a limited heat of reaction. If ΔH for the transition are positive (endotermic reaction), the temperature of the sample will lie behind that of the reference (because more heat will be absorbed by the sample than by the reference) and this event will be recorded in the thermogram as a negative spike. If the ΔH is negative (exoermic reaction), the temperature of the sample will exceed that of the reference (because the sample itself will be a source of additional heat) and the event will be recorded in the thermogram as a positive spike. Thus, DTA analysis is an excellent qualitative technique that is useful in in informing the temperature ranges associated with a variety of thermal events, as well as enhanced the endotermic or exoermic nature of these reactions. An astonishing number of studies have been published where DTA analysis has been used to characterize the characteristics of a wide range of materials, so only a single example will be given here. The characteristic transition temperature of DTA endotermics obtained for evaporating 2,4-difluoronitrobenseen as a function of pressure was used to obtain the phase diagram of this substance. A family of these DTA thermograms is found in Figure 7.FIGURE 7. DTA endoterms obtained for evaporation of 2,4-difluoronitrobenzene as a function of pressure. Differential scanning calorie (DSC) represents an improvement to DTA analysis, and has become one of the most widely used methods of thermal analysis. In the DSC method, the sample and the reference are kept at the same temperature and the heat flow required to maintain the equality in temperature between the two is measured.51 This equality can be achieved by putting separate heating elements into the sample and the reference cells, where the rate of heating is controlled and measured by these elements. This method of meting is called power compensation DSC, and (as opposed to IUPAC guidelines) it delivers positive-going peaks for endotermic transitions and negatives going peaks for exoermic transitions. Another methodology is that of heat-flood DSC, where the sample and the reference cells are heated by the same element, and the direction and size of the heat transmitted between the two is monitored. Heat-flood DSC is likely a preferable method drenched baselines relative to those obtained using power reimbursement DSC. In addition, negative peaks are obtained for endotermic transitions positive peaks are obtained for exoermic exoermic (same as for DTA analysis) that is in tune with the IUPAC guidelines. DSC erven are obtained as the differential rate of heating (in units of watts per second, calories per second, or Joules per second) at temperature, and thus they represent direct measures of the heat capacity of the sample. The area below a DSC peak is directly proportional to the heat absorbed or developed by the thermal event, and integration of these peak areas delivers the heat of reaction (in units of calories per second per gram or Joules per second per gram). Due to the ability to facilitate quantitative data interpretation, the use of DSC analysis has virtually supplanted the use of DTA analysis. When a compound is observed to melt without decomposition, DSC analysis can be used to determine the absolute purity.52 This method can therefore be used to evaluate the absolute purity of a given compound without reference to a standard, with purities obtained in terms of mole percent. The method is limited to fairly pure compounds that melt without decomposition, because the assumptions that justify methodology fail when the compound purity is less than about 97 moles%. One other commonly used thermoanalytic technique is that of thermogravimetry (TG), where the thermally induced weight loss of a material is measured as a function of the applied temperature.53 TG analysis is limited to studies involving either a mass gain or loss (usually loss), and is most commonly used to release processes and compound decomposition The main use of TG analysis is the quantitative determination of the total erraous content of a solid. When a fixed solid can dissolve through various discrete, sequential responses, the scope of each step can be evaluated separately. TG analysis of compound decomposition can also be used to compare the stability of similar compounds. The higher the decomposition temperature of a given compound, the more negative ΔG value and thus the greater the stability. An example will be cited to illustrate the synergistic relationship that exists between DSC and TG analysis. The anhydrate, dihydrate and trihydrate phases of chemically pure magnesium stearate and magnesium palin palmitaat were prepared and characterized over their structural properties.54 The crystal structures of the different materials were found very similar to each other, which differ mainly in the range of long (001 face) crystal spacing. The full thermal characterisation of magnesium stearate hydrate is shown in Figure 8. The nature of the lowest temperature endotermic transition seen in the DSC thermogram was established as a dehydration transition, because a substantial weight loss observed to occur over the same temperature interval. On the other hand, the temperature endothermic transition in the DSC thermogram confirmed as a melting transition because this event occurs without any loss in mass. FIGURE 8. Differential scanning calorythiatrics (bottom rail) and thermogravimetry (upper rail) thermograms obtained for the dihydrate phase of magnesium stearate. The data was adjusted from reference 54.Walt Morozowich, Ping Gao, in developing solid oral dosage forms, 2009 This section reviews the scientific literature on SEDDS/S-SEDDS formulations over the past ten years from 1998 to 2008, and summarizes the key publications dealing with both: 1.developing and characterizing SEDDS/SEDDS formulations; and2.the determination of the oral bioavailability of the resulting SEDDS/S-SEDDS formulations of poor soluble agents in preclinical and clinical studies. The first quote in PubMed took place in 1992, and by the end of 2007 the cumulative number of quotes was 34 for the search terms SEDDS or S-SEDDS. Most of these quotes were also found in a PubMed search for self-emulsification formulations, where the total number of quotes was 101. However, these search results included many publications that did not deal with the development of SEDDS/S-SEDDS formulations and oral bioavailability. The 34 quotes in the PubMed search for SEDDS or S-SEDDS are briefly reviewed chronologically in the following text. Using danazol as a model connection, SEDDS formulations are prepared with Cremophor RH40 or Cremophor EL, and long chain triglyceride. It was concluded that the key design parameters for efficient oral absorption of danazol from lipid-based formulations were: (a) rapid distribution of the formulation against dilution with water; and (b) rapid intestinal digestion or hydrolysis of the triglyceride excitement by pancreatic enzymes.1Self-emulsifying delivery systems is useful for improving the absorption of poor soluble lipophilic drugs. The drug absorption mechanism has been revised, and the in vitro testing methods found useful in formulation design are formulation compatibility and digestibility of the surfactant and lipid in vain.2SEDDS formulations of alpha-tocopherol containing polysorbate 80, Labrasol, EtOH and Captex 355 are subjected to lipase-catalyzed hydrolysis in biorelevant media to determine the effect of excitement on the rate and extent of hydrolysis. The authors found that: the excitement affected each response differently and therefore each method can only reveal distinctive features of the SEDDS formulation, and may not be used interchangeably.3Two SEDDS formulations of probucol with the same composition, but with a 100-fold difference in particles size, comparable oral bioavailability in fed or fasting minipigs.4Table 19.1 shows the main surfactant-lipid formulations reported in the literature with poorly soluble drugs.5 The table shows that many of the drug-lipid formulations, such as the SEDDS formulations, such as the SEDDS formulations. the absorption of a variety of poor water-soluble drugs. Table 19.1. Survey of SEDDS formulations and their reported bioavailables.5 Examples of studies studies die biobeskikbaarheidsverbetering van PWSD na toediening van SEDDS en SMEDDS formuleringsCompoundFormulation(s)Studie designObservationsWin 54954SEDDS (35% dwelm, 40% Neobee M5 (MCT), en 25% Tagat (TO) of PEG 600 oplossingRelative BA in dogsNo verskil in BA, maar verbeterde reproduktiwiteit, verhoogde CmaxCyclosporinSandimmum (SEDDS: mielie-olie en etanol) of Neoral (SMEDDS: koring olie gliseriede, Cremophor RH40, PG DL-α-tocopherol en etanol)Relatiewe BA in menseIncreased BA en Cmax en verminder Tmax van SMEDDSSandimmum (SEDDS) of Neoral (SMEDDS)Relatiewe BA in mensIncreased Cmax, AUC en dosis linieariteit en verminderde voedseleffek van SMEDSSSandimm) of Neoral (SMEDDS)Relatiewe BA in menslike Intra- en intervakvergeskiktheid SMEDDSHalofantrine5% dwelm in MCT SEDDS (47% Captex 355, 23% Capmul MCM, 15% Cremophor EL en etanol), MCT SMEDDS (33% Captex 355 , 17% Capmul MCM, 33% Cremophor EL , en etanol), of LCT SMEDDS (29% Sojaboonolie, 29% Maisine 35-1, 30% Cremophor EL, en 7% etanol)Relatiewe BA in hondeTrend om hoër BA van LCT SMEDDSOntazolastSoy dwelm oplossing in Peceol, dwelm skorsing of twee semi-soliede SEDDS bestaande uit Gelucrie 44/14 en Peceol in die verhoudings 50:50, en 80:20Absolute BA in ratsBA verhogings van ten minste 10-vou van alle lipiedgebaseerde formuleringsVitamin ESEDDS (Tween 80:Span 80:palmolie (LCT) in 'n verhouding van 4:2:4) of sojabone olie (LCT) in oplossingRelatiewe BA in humansBA 3-vou hoër van SEDDSCoenzyme Q10SMEDDS (40% Myvacet 9–45, 50% Labrasol, en 10% luaroglycol) of poeier formuleringRelatiewe BA in hondeBA 2-voudig hoër van SEDDSRo-15-0778SEDDS (poliglycolyzed glycerides en grondboontjieolie) , PEG 400 solution, wet-milled spray dried powder or tablet of micronized drugRelative BA in dogsBA 3-fold higher from SEDDS when compared with other formulationsSimvastatinSMEDDS (37% Capryol 90 , 28% Cremophor EL, 28% Carbitol) or tabletRelative BA in dogsBA 1.5-fold higher from SMEDDSBiphenyl dimethyl dicarboxylateSEDDS(43% Tween 80, 35% triacetin, and 22% Neobee M-5 (MCT)) or powder formulationRelative BA in agileBA 5-fold higher from SEDDSIndomethacinSEDDS (70% ethyl oleolate and 30% Tween 85) or powder formulationRelative BA in agileBA significantly increased from SEDDSProgesteroneSEDDS (mono-di-glycerides:polysorbate 80, 50/50 w/w) or aqueous suspensionRelative BA in dogsBA 9-fold higher from SEDDSTocotrienolsTwo SEDDS (Tween 80 and labrasol) or LCT solutionRelative BA in humansBA 2- to 3-fold from higher of SEDDSDanazolLC-SMEDDS (long chain lipids , Crem and ethanol), MC-SMEDDS (medium chain lipids, Cremophor EL, and ethanol) or LCT solutionRelative BA in dogBA of LCT solution and LC-SMEDDS 7-fold and 6-fold higher than that of MC-SEDDSCarvedilolSEDDS (labrafil M1944CS , Tween 80 and transcutol), and tabletRelative BA in dogsBA 4-fold higher of SEDDSSolvent green 3Semi-solid SMEDDS (Gelucrine 44/14) or soybean oil emulsionRelative BA in ratsBA 1.7-fold higher of SMEDDSilymarinSMEDS (Tween 80 expand higher (Tween 80, folds higher out of SMEDDSilymarinSMEDS SMEDDSilymarinSMEDS en ethyl linoleate), PEG 400 solutionRelative BA in konyneBA ongeveer 2- en 50-voudig hoër uit SMEDDS as dié van PEG 400 oplossing en sksorsingAtorvastatinThree SMEDDS (Cremophor RH40, propylene glycol, en labrafil, estol of labrafac) of tabletRelative BA in hondeBA aansienlik toegeneem van alle SMEDDS formuleringsItroconazoleSEDDS (Transcutol, pluronic L64, en tocopherol asetaat) of konvensionele kapsuleRelative BA in ratsIncreased BA en verminderde voedseleffek van SEDDSAtovaquoneTwo SMEDDS etanol, en Cremophor EL of Pluronic L121) of waterige sksorsingRelatiewe BA in hondeBA 3-vou hoër van SMEDDSSeocalcitolLC-SMEDDS (sesame olie, Peecol, Cremophor RH40) teenoor MC-SMEDDS (Viscoleo MCT), Alkoline MCM (medium ketting mono- en di-gMEDDS (Viscoleo MCT), Alkoline MCM (medium ketting mono- en di-gMEDDS (Viscoleo MCT), Alkoline MCM (medium kettingmono- en di-gMEDDSlyceride) en Cremophor RH40Absolute BA in ratsBA LC-SMEDDS=MC-SMEDDSPNU-91325Supersaturable mede-oplosmiddel (S-mede-oplosmiddel) en supersaturable SEDDS (S-SEDDS bestaan uit 20% HMPC , 30% Cremophor EL , 18% Pluronic L44, 9% PEG, 6% long chain glyceride lipid, 5% DMA) formulations compared to co-solvent (PG) or Tween 80 solutionsRelative BA in agile5-6-fold improvement in oral bioavailability S-SEDDS, and Tween 80 formulations relative to co-solventItraconazoleSEDDS formulation consisting of Transcutol, Pluronic L64, and tocopherol acetate versus commercial Sporanox formulationRelative BA in agileIncreased BA and reduced food effect from SEDDS7 model compounds, including disopyramide ibufed ketoprofen, and tollutamideComparison of PEG 200 solution and suspension formulations to SEDDS (consisting of 25% MCT, 5% diglycerylmonoleate, 45% Cremophor RH40, 25% Ethanol), and liquid microemeulsion (consisting of 5% MCT, 1% el % Cremophor RH40, 5% Ethanol, and 80% phosphate buffered salt)Relative BA in rats and dogsImproved BA relative to the suspension formulations for either or both of the liquid microsemeulsion and SEDDS formulation in all casesThe literature on SEDDS formulations of poorly soluble drugs and oral bioavailability , and it has been concluded that improved oral bioavailability is best achieved using screens for distribution, lypolying of triglycerides, and digestion of surfactants.5In a comprehensive review of lipid formulations that contain surfactants, such as SEDDS/S-SEDDS, It was said that the key role of these formulations was to improve the solubility of the drug in the formulation and in the GI channel.5aFigure 19.2 shows that distribution of a lipid surfactant SEDDS formulation occurs in the stomach, and this spread can equilibrium with the bile salt/phospholipid micelle. Lipid and surfactant hydrolysis products are formed in the small intestine by lipolytic pancreatic enzymes. Figure 19.2. Cartoon showing the main physiological and biochemical events that with a lipid-surfactant-drug formulation like a gelatinous softgel formulation of a poor water-soluble drug. The lipolytic enzymes (pancreatic lipase) stored in the gallbladder gallbladder the duodenum and they hydrate the long chain triglycerides (LCT) to give 2-mono-acyl glyceride. The resulting BA and BAMM particles may be equilibrium with the drug-SEDDS microemulsion followed by intestinal absorption of the drug.5A decision support tool was developed for ories active poor soluble compounds, based on the proposed formulation selection process,6 as shown in Figure 19.3.Figure 19.3. Decision-making tree for the guidance of formulation decisions (Branchu, 2007)Figure 19.3 shows the three key decision points in formulation development. The authors concluded that the decision support tool has great potential for improving the efficiency and predictability of the formulation development process. Figure 19.4 shows that the reported increase in the aqueous solubility of danazol (a) in Cremophor RH40 does not lead to improved oral bioavailability of danazol (b).5Figure 19.4. The effect of lipolitic digestion of the Cremophor RH40 and Cremophor EL formulations of danazol. Left: (a)—the watery phase levels of the danazol formulations and right: (b)—the danazol plasma levels of these formulations in the dog. Formulation 1: The Cremophor RH 40 SMEDDS contains 55% w/w Cremophor RH, 37.5% w/w soybean oil/Maisine, 7.5% w/w ethanol. Formulation 2: The Cremophor EL SMEDDS contains 55% w/w Cremophor EL, 37.5% w/w soybean oil/Maisine, 7.5% w/w ethanol. The lower digestibility of Cremophor RH40 leads to higher bioavailability.5In a previous study, increasing the surfactant-to-lipid ratio was found to reduce the oral bioavailability of danazol in dogs.8 The increase in drug solubility observed during in vitro digestion led to increased oral bioavailability of danazol. Interestingly, the oral bioavailability (in beagle dogs) was highest with a soybean Maisine-Cremophor EL microemulsion generation formulation, and the lowest with a formulation containing Cremophor without soybean Masine.A study of the effect of small amounts of lipids on stomach emptying and biliary secretion showed that oral administration of as little as 2 gm of glycerol monoolyate (GMO) (in healthy men) led to stimulation of biliary secretion of biliary secretion of biliary secretion. The same amount of medium-chain triglycerides (MCT) (Miglyol 810) failed to cause the slump of the gallbladder, and did not lead to secretion of bile. The authors pointed out that the amount of lipid, namely 2 gm GMO/MCT, is a quantity that can realistically be expected on application of 2×1 g of soft gelatin capsules. Moreover, it suggests that administering 2×1 g G GMO in soft gelatin capsules with a drug in a clinical study in the fasting state could lead to drug absorption that mimics the fed state.9 Developing lipid-based formulations has been reviewed10 regarding: excited classes (natural product oils, semi-synthetic lipid excitement, fully synthetic excitement, and surfactants); 2.formulation types and modities (single component lipid lipid self-emulsifying formulations, and melting correlation);3.formulation development and characterization, including drug candidate selection, excited compatibility, selection of a formulation modity, physicist-chemical consideration, biopharmaceutical consideration, in vitro characterization, in vitro decomposition testing, and role of lipolie in release test. The authors10 acknowledge that due to the complex and incomplete understanding dynamics of the interaction of formulations with the digestive pain milieu, animal bioavailability studies must precede clinical studies. The main advantages of lipid-based formulations are: 1.reduced change;2.reduction in the number of formulation-based processing steps;3.reduction in positive food effect; and4.the ease of formulation manufacturing and scale-up. The use of lipid-based formulations for improving drug absorption has been revised in relation to the mechanisms responsible for improved oral absorption.5 The concentration of bile salts in the vilified state in the duodenum/jejunum is ~3-4 mM, while the bile salt concentration in the fed is ~10-16 mM. These increased concentration of bile salt in the fed state are responsible for increased drug solubility. With poor soluble agents, improved oral bioavailability is often observed in the fed state. The soluble property in the fed state is due to the presence of the bile acid mixed micelle (BAMM). The review of the lipid absorption path.5 indicated that highly lipophilic drugs can show significant limphatics. Figure 19.5. Cartoon showing that lipid-based drug formulations can improve drug absorption through drug solubility in the resulting micellar phases, mainly the bile acid mixed micelles arising from bile. Highly lipophilic drugs can undergo limphatic uptake, thereby by byting first pass liver metabolism.5 Using surfactants as enterocyte P-gp pump inhibitors (Table 19.2) have been reviewed, and improved oral absorption has been documented with a number of drugs using this strategy.11Table 19.2. Surfactants with P-gp inhibitor activity11SurfactantsC8/C10 Glycerol and PEG Esters, Cremophor, Solutol HS-15, Labrasol, Softigen 767, Aconnon ESucrose Esters, Sucrose MonolauratePolysorbates, Tween 80, Tween 20Tocopherol Esters, α-Tocopheryl PEG 100 Succinate (TPGS)The discussion with the use of P-GP inhibitors is that intestinal absorption of undead in addition, P-GP inhibitors have pharmacological activity of their own and, therefore, P-GP drug combinations can lead to improved side effects. The effect of administering a high fat meal (peanut oil) or plain water on the plasma levels of DDT in rats was studied.12 The resulting plasma profiles for DDT (oral) were much higher after oral administration of peanut oil, compared to oral administration of ordinary water. The plasma levels of diazepam (oral) were practically the same after oral oral peanut oil or water. This data suggests that diazepam is probably not absorbed by the intestinal mucotics after oral administration, but DDT is, and it is consistent with the literature.12The usefulness of microsemeul-genating formulations in improving the oral absorption of poor soluble drugs has been reviewed. The main considerations in the development of SEDDS formulations that can generate a microseedetection at contact with water are: (1) surfactant; (2) co-surfactant; and (3) oils. The use of nitrendipine formulations consisting of: (a) medium-chain triglycerides; (b) triglyceride suspension (c) long-chain triglyceride solution, and (d) Tween 80, were shown to have been the resulting Tmax values in a fixed human clinical study 8, 4, 1.3 and ≥8 hours, respectively. The Tmax values in the fed state in the same clinical study resulted in Tmax values of 1.5, 3.5, 1.3, and ≥7 hours.13 This data is significant, permotive that the Tmax of nitrendipine was reduced to 1.5 hours in the fed state, compared with 8 hours in the fasting condition. A nanoemulsion-genating formulation of paclitaxel was developed using 1920 mg labrasol plus vitamin E-TPGS (3:1), 80 mg Labrafil M1944CS, and 20 mg paclitaxel.14 Dilution of the formulation with water led to the formation of a nanoemulsion

with a particle (glowing) size of 21.58 pm, which is in the range of many microemulsion-genating formulations. The rat oral bioavailability (absolutely) of paclitaxel from this nanoemulsion formulation is reported to be 70.25%. The absolute rat oral bioavailability of paclitaxel of the Taxol® IV formulation was only 10.62% and < 30% for an S-SEDDS formulation of paclitaxel. The effect of fasting (FaSSIF) and fed (FeSSIF-Mod 6.5) state (Table 19.3) on the absorption (in dogs) of danazol from a self-emulsifying formulation was found in excellent agreement with the higher solubility of danazol in the FeSSIF, compared to the FaSSIF.15 15. Composition of simulated intestinal fluids17pHTauro- cholateLecithinmOsmSimulated intestinal fluidFaSSIFa6.53 mM0.75 mM270+10FeSSIFb5.015 mM3.75 mM635+10Simulated intestinal fluidFaSSIF-Modc6.53 mM0.75311.7+0.6FeSSIF-Mod5.0d5.015 mM3.75 mM327.0+1.0FeSSIF-Mod6.5e6.515 mM3.75 mM325.7+0.6The oral bioavailability of itraconazole in a SEDDS formulation containing transcutol, pluronic, and tocopherol acetate was found to give an AUC (oral) similar to that of the marketed Sporanox® product, however, the Tmax was 1.3 hours for the SEDDS formulation , and 8 hours for the Sporanox® product.16The oral bioavailability of the naphthalene analog, Ro 15-9778, either in a SEDDS formulation, a PEG 400 solution, a spray threed powder or a tablet formulation, showed a relative anywhere bioavailability (in dog) or 389, 100, 35, and 17%, respectively. The self-spreading SEDDS formulation gave better oral bioavailability, in with the alternative conventional formulations.18In a review of the oral absorption of drugs into SEDDS formulations, it was it that bioavailability depended on the surfactant concentration, and the polarity of the resulting emulsion/micro-fertilization formed on dilution with water, the droplet size and the load. The rat oral bioavailability of the highly lipophilic compound seocalcitol was roughly the same in SEDDS formulations and in simple triglyceride solutions, indicating that highly lipophilic drugs may not require SEDS formulation for maximizing oral bioavailability.19The mechanism of intestinal survey of drugs and drug formulations has been addressed in a large number of papers by Charman, Porter and collaborators. These publications included the solubility of poor soluble drugs in the GI channel after administration of lipid-based drug delivery systems, eurs that provide the digestion and distribution of the lipid vehicle a solubility thinking that can prevent precipitation of the poor soluble drug.20 A study on the factors that lemphatic absorption of poor soluble drug can occur.20 A study on the factors that lemphatic absorption of poor soluble drug can occur. showed that the lymph-lipid pool is a key determinant of intestinal lymphatic drug transport.21,22 The physicist-chemical properties of halofantrine, such as log D versus pH dependence, have been found to explain the extensive olympic transport of halofantrine in the fed state. At a pH below 2, the log D is of halophrine<0, but since the pH is increased to ~7, the log D is increased to ~3 in watery Post-taurocholate-lecithin (4:1). The high lipophilicity of halofrine at pH ~7 suggests high affinity for the lymphatic system.23In a review of the lymphatic delivery of drugs, the exceptionally high log P values of itretinate (7.8), and isotretinoin (6.8), are responsible for the extensive lymphatic delivery.24 The effect of the fatty acid binding protein (FABP) on the enterocyte uptake of fatty acids showed that the FABP can be a determinant of lymphatic drug transport.22A microemulsion-generating formulation was prepared using MCT, DGMO-C, HCO-40, and EtOH, in the ratio of 5:1:9:5 (v/v), and this SEDDS formulation was found to improve the oral absorption of 10 drugs, including ibuprofen, ketoprofen, tamoxifen, testosterone, and tolbutamide, in addition to other new drugs.25An emulsion generating formulation of cyclosporine was developed with an oat galactolipid and MCM (1:1).26 Dilution of the formulation with water gave a particle size ~3 µm (an emulsion) , while dilution of the Neoral formulation of cyclosporin has a particle size of 10-20 pm (a microsemulsion). A clinical study showed that the oral bioavailability of the galacolipied cyclosporin formulation, compared to the Neoral® formulation, was practically the same, as evidenced by the Tmax and AUC values. Both formulations showed a Tmax of ~1.5 hours. The Neoral ® SEDDS formulation of cyclosporin was the first marketed microsemeulation-generated formulation in the pharmaceutical industry. Dilution of the Neoral® with water leads to a rapid formation of a transparent solution, typical of a microsemulsion, with blue cast, and a particle size of ~20 pm. Figure 19.6 shows the oral bioavailability of the Sandimmune ®-generated formulation, Together with the improved Neoral microemulsion-genating formulation of cyclosporin in a non-transplant patient.27,28 The Sandimmune® SEDDS formulation contains long-chain triglycerides, with a surfactant and the lipopholic compound, cyclosporin. The absorption of cyclosporin from the Sandimmune® formulation occurs after partial hydrolysation of the long-chain triglyceride, and it can be a slow process, as shown by evening dosing blood level curve (SIM p.m.), which shows a peak at 8 p.m. The peak blood levels of cyclosporin after morning dosing (SIM a.m.) show a somewhat shorter peak at 4 hours. However, the Neoral ® shows a peak in the blood-level curve for cyclosporin at ~1.5 hours in the fasted state, and 1.2 hours in the fed state. The resulting AUC for the Neoral® formulation is greater than that of the Sandimmune® formulation, as indicated in Figure 19.6. There is virtually no food effect (AUC = 997, fasting, and AUC = 892, fed) with the Neoral® formulation. The superiority of the new microemulsion-generated Neoral formulation of cyclosporin has been confirmed in extensive clinical studies.29,30Figure 19.6. Representative cyclosporin blood concentration profiles of a non-transplant patient given the currently marketed formulation Sandimmune® (SIM) or the new Neoral® formulation without food (a.m.) or with food (p.m.). Poor soluble agents can be improved in SEDDS formulations with formulation designed to give a submicron-sized colloidal condition against dilution with water.2 Knowledge of the effectiveness of self-emulsification on contact with water, the susceptibility to the digestion of the surfactant excitement, as well as the lipid triglyceride excited, and the subsequent fate of the drug is useful in optimizing the formulation.2 Studies on dermabsorption of lipids and, Especially cholesterol, established the key role of the bile acid mixed micelle (BAMM) in the oral absorption of lipophilic compounds.31–34,7There were four papers dealing with SEDDS/S-SEDDS formulations in 1997. The requirements for comphatic transport have been developed, and it has been concluded that the log P of the drug should be high (>6), and the drug should be soluble in triglycerides, in order to achieve effective mucous plymphatic absorption. The development of SEDDS formulations has been revised in detail regarding the factors that affect ease of emulsification.35 SEDDS formulations usually contain triglycerides, along with PEG surfactants, with surfactant concentrations greater than 15%. The first paper found in the PubMed search on SEDDS or S-SEDDS was published in 1992, dealing with an SEDDS formulation of the poor soluble drug, WIN 54954.35 The part size of the about dilution with water wash <3 µm. The SEDDS formulation has higher AUC in the dog dog A PEG 400 solution. Solution.