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WHITHER COMPATIBILITY TESTING?

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ABSTRACT

Excipient compatibility studies are of limited value in the selection of ingredients which will provide a stable dosage form. These empirical tests are often substituted for estimates of potential instability based on known chemical interactions. They are inefficient, and their predictive value has not been rigorously established. It is more meaningful and economical to prepare initial formulations for stability screening than to test for excipient compatibilities in powder mixtures.

INTRODUCTION

There are many reasons why excipient compatibility testing is of limited value for excipient selection in the preparation of a dosage form. Based on an excipient compatibility test, a valuable excipient may be discarded which would present neither a physical nor a chemical problem in the final formulation. Conversely, history has indicated excipients may be selected for formulating a compound based on excipient-drug testing but they will cause a physical or chemical interaction, directly or indirectly, in the dosage form.

The preparation of excipient mixtures is very time consuming, and compatibility tests address a limited number of variables. Excipient-to-drug ratios only approximate those of a dosage form; mixtures of drug and multiple

excipients are seldom examined; processing effects are ignored. A stability indicating assay must be developed and then applied to measuring content uniformity and analyzing each mixture after storage under various conditions. This entire process takes considerable time and resources to yield information that is still only a crude predictor of formulation stability or instability.

Before designing a dosage form, the formulator must consider the structure of the drug and the site of delivery desired. The initial step should consist of choosing excipients having the appropriate delivery characteristics. Potential interactions between those and the drug should be considered based on knowledge of the chemistry of the classes of compounds involved. Reactivities of commonly used excipients have been published[1]. From a brief review of the pertinent literature a logical choice of initial formulations may be made[2].

It is more realistic and efficient to perform mini-formulation studies. The proposed dosage form may be prepared on a small scale. The availability of sophisticated small-scale manufacturing equipment, such as compaction simulators, allows examination of variables which are ignored in classic compatibility studies. The use of such equipment offers the advantage of identifying and controlling manufacturing influences on dosage form stability.

HISTORY

The effect of excipients on pharmaceutical stability appeared in the literature as early as the mid-1950's. The earliest studies examined only physical appearance. Attempts were made to formalize visual observation by developing appropriate scoring systems; a refinement was tristimulus reflectance measurements[3]. As analytical techniques were developed for monitoring stability of the drug substance, they were applied to excipient compatibility testing. Recommendations to perform the studies prior to making a dosage form became common.

The sophistication of pharmaceutical manufacturing processes has increased dramatically within the past thirty years[4]. Historically, processing effects may not have been significant. Now, however, in addition to higher pressure, wet granulation, etc., new types of compounds are being formulated,

such as proteins, peptides, and enzymes. More complex formulations are being manufactured in attempts not only to improve bioavailability, but also to reduce toxicity, and to effect site specific drug delivery.

When the problem of dosage form stability was recognized, compatibility testing was a first attempt to address it. However, application of the technique has continued beyond its useful life, and in light of current knowledge it has become obsolete.

CURRENT FACTS

In the typical compatibility testing program, binary powder mixtures are prepared by triturating the drug with individual excipients. These powder samples, one set of which is generally moistened, are stored under accelerated stability conditions and analyzed by the stability-indicating method developed for the drug. Some investigators recommend examining compacts or slurries[5]. Alternatively, samples may be analyzed immediately by methods such as differential thermal analysis (DTA) or differential scanning calorimetry (DSC). By eliminating the stability setdowns, time and sample consumption are reduced. Results of such rapid-scan analyses, however, may be misleading. In some cases they indicate incompatibilities which may not actually exist, whilst in others they have failed to detect or predict interactions. Another approach to reducing the effort is through statistical design. 'One-factor-at-a-time' methods have been supplanted by factorial design or reduced factorial design experiments.

Compatibility studies are often used as a substitute for prediction of potential instability based on established chemical interactions. Knowledge of potential chemical interactions should lead to the judicious selection of excipients prior to initiation of lab work. Before any formulation is started, many physical and chemical properties of the compound will be known from preformulation studies. Based on these data and the structural features of the compound, many potential interactions with certain excipients can be deduced. Some of the most widely used excipients are quite reactive. For example, if the compound has a primary amine function, all monosaccharides and even disaccharides should be excluded from the formulation (amine-aldehyde and

amine-acetal reactions). Graf et al have published a stability study in which enzyme tablet formulations developed brown spots. After storage for about seven months at 37°C, those including Emdex 'showed inner and outer brown spots, apparently caused by a Maillard reaction of the aldehyde groups of glucose, the main component of Emdex, with primary amino groups of the enzymes.' In addition, the enzymatic activity of the tablets was vastly reduced[6]. When the compound is an ester or lactone, of course, all excipients which can produce a basic environment must be avoided (ester-base hydrolysis). The formation of hydrogen bonds, such as those between carbonyl and silanol groups, may destabilize a drug. Such an interaction enhances the oxidative degradation of linoleic acid methylester (LME) at the surfaces of porous and colloidal silicas and colloidal aluminum oxide[7]. Obviously, any compound containing an aldehyde moiety should not be mixed with amine type excipients (aldehyde-amine reaction). Also, any easily hydrolyzable drug[8] should not be mixed with a hydrated excipient if the water of crystallization can be released by the formulating process. Neither should it be combined with hygroscopic excipients; these will contain varying moisture contents depending upon environmental conditions. Methylcellulose forms molecular associations with organic acids; the stability depends on the pKa of the acid[9]. Adsorption of drugs to various celluloses has been shown to depend on the degree of hydrolysis of the cellulose; the reversibility of the adsorption is pH dependent[10].

Once the types of excipients to be used are chosen, the formulator should be aware of the potential for catalysis of degradation by impurities in them. Ferric iron catalyzes the oxidation of drugs such as hydrocortisone. Clays containing adsorbed ferric iron should be avoided in formulating drugs prone to such oxidative degradation[11].

It is well known that lubricants may interfere with release rates of drugs from dosage forms. Lubricants have also been found to have a deleterious effect on solid state stability. Compression forces liquefy low-melting lubricants, which then dissolve the drug. Magnesium stearate is a notoriously problematic excipient, and its properties have been the subject of much research. Ertel and

Carstensen recently examined the physical structure and properties of the pure material[12].

Certain excipients should be considered for inclusion in initial formulation screening based on structural features of the compound, e.g., antioxidants with easily oxidizable drugs containing thiol or phenol groups. The use of polymeric excipients to protect drugs from moisture and oxygen has been reported[13]. Polyacrylate and polymethacrylate were used to prevent interactions of a model drug with other tablet components and with moisture. Arachidonic acid is a compound which oxidizes readily. Some components commonly used in topical preparations were found to inhibit this reaction[14]. Petrolatum, mineral oil and certain lipid-containing emulsifiers, such as aloe gel, reduced in vitro oxygen consumption. Jacobs has reported improved stability of an experimental steroid in tablet formulations versus the undiluted drug[15]. The success of this approach to excipient selection based on potential interactions is limited only by the scientific knowledge, imagination, and intuition of the investigator.

DEFICIENCIES OF THE TEST

As compatibility studies are typically executed, scientific and economic deficiencies exist. The test addresses too few variables, excludes processing effects, and has poor predictive value. It is labor intensive and time consuming. Compatibility studies increase the development time of new drug products. The scientific literature contains many reports of results of compatibility studies, but the unsuccessful studies tend to remain unpublished.

The poor quality of the model is a major disadvantage; simple mixes with one excipient do not address addition or competition effects or account for processing. The recommended protocols for performing excipient compatibility studies are numerous. The usual method is preparation of individual mixtures of the drug with each excipient under consideration. The ratio of drug-to-excipient is often one to one, but may range from one to five or twenty to one[3, 16-19]. Ingredients which comprise a minor portion of the final dosage form are sometimes excluded from testing in order to reduce the number of samples.

An example of an interaction between a flavor enhancer and other tablet components illustrates this pitfall. An attempt to reformulate a British product

for the American market included routine drug-excipient compatibility studies. Tablets which were subsequently prepared and placed on stability developed brown spots. On examination it was determined that a commonly used flavor enhancer had interacted with an alkaline excipient. The flavor enhancer consisted of oils spray dried onto a carrier, and in the alkaline tablet environment the oils had separated and formed the spots. This was not a drug-excipient interaction and, therefore, it was not predicted by compatibility studies.

The preparation of excipient mixtures is very time consuming; weighing and mixing by trituration each excipient and drug combination is labor intensive. A stability-indicating assay must be developed and then applied to measuring content uniformity and assaying each mixture after storage at various temperature and humidity stations. This entire process takes considerable time and resources to yield information that is still only a crude predictor of formulation stability/instability.

In the development of SK&F 86466, a classic compatibility study was performed and no instability was found. Formulations were less stable, and the problem was exacerbated at lower dosages. Approximately a 15% loss of active was seen in one mg capsules which had been stored for one year at 30°C. Comparable results were found for tablets. A similar type of problem occurred during the formulation of lower dosages of Captopril. In neither case did the compatibility testing predict these problems. Enalapril maleate exhibits decreased stability in the presence of excipients. Cotton et al determined that an interaction occurs between the drug and microcrystalline cellulose which depends on the drug-excipient ratio and the surface contact between them. They theorize that the interaction alters the drug's crystal structure[20]. Routine compatibility studies may detect such an instability, but they provide little information toward solving a problem of such complexity. Ibuprofen is known to form eutectics with excipients and it sublimes.

Homogeneity of powder samples is sometimes difficult to achieve and may cause erratic analytical results. Powder mixes of SK&F 86002 and individual excipients were prepared by trituration. Assay values for the mixes

were found to vary (±5%) in a random fashion suggestive of non-uniformity of mixing. A similar problem was seen when SK&F 39162 tablets were ground prior to analysis. Density, particle size, and static charge of the components, as well as the type of excipient, influence the ability to achieve a uniform mixture[21]. In a mixing study on binary mixtures containing small quantities of cyclopenthiazide as a model drug, a segregation effect was observed with both coarse and fine lactose[22].

Whether an incompatibility is found with an excipient is often dependent upon the drug-to-excipient ratio. The excipient concentration that will be necessary in the formulation is often not known, and an arbitrary excipient to drug ratio is chosen for stability evaluation. Since any physical or chemical reaction under the stress conditions will be different with varying drug concentrations, the value of stability data obtained with one concentration is open to question. Also, the drug concentration in the formulations can vary greatly with initial clinical studies with high dose ranges. It is, of course, impractical to test many drug-excipient ratios in excipient compatibility studies. Even a high/low approach will double the effort, e.g., ten excipients result in 10! mixtures.

Reduction of the number of samples by rational design of the study has been the subject of many papers on compatibility testing. Models proposed include factorial design[23,24], fractional-order randomized block design[25], selective regression analysis[26], and other methods used for dosage form stability studies[27].

Drug instability can be the result of multiple excipient interactions. These physical and chemical changes occurring between multiple excipients during stress testing can alter their compatibility with the drug. The testing of many combinations of excipients with the compound is impractical.

The processing method used to formulate can greatly affect excipient-to-excipient and drug-to-excipient interactions either positively or negatively, which invalidates the conclusions based on excipient compatibility testing of powders. Solid state properties of drugs and excipients can be altered by the mechanical manipulation necessary for formulation of dosage forms. Increased

drug-excipient contact due to compression can greatly alter physical or chemical stability. For example, compacting aspirin with dicalcium phosphate dihydrate can greatly accelerate aspirin hydrolysis compared to aspirin powder alone or mixed with dicalcium phosphate dihydrate even when stored at very low humidity conditions[5]. This difference in reaction rates could be due to the release of hydrated water from the dicalcium phosphate at compaction which would readily promote aspirin hydrolysis because of the intimate contact between the compounds. Stanley-Wood and Johansson have examined the relationship between adsorption forces and compaction pressure[28]. Lach and Bornstein have observed spectral and physical changes after compression of samples. They found the intensity of these changes proportional to the pressure applied[29]. In a study of the solid-solid interaction between alkoxyfuroic acids and microcrystalline cellulose, it was determined that the decomposition of the mixture differs from that of the drug(s) alone[30]. To compare mixing effects, three techniques were used to prepare the drug-excipient samples: quartering, grinding in a ball mill or by mortar and pestle, and suspension in and subsequent evaporation of a solvent. The ground samples were least stable, and the solvent-deposited samples were more stable than the simple mixtures.

The exposure to moisture is greatly different when powders, tablets or capsules are exposed to stress conditions. Labile hydrates, such as dicalcium phosphate dihydrate, can dissociate to liberate free water. Accelerated testing of moisture-sensitive drugs in the presence of such materials could indicate an instability which would not exist under normal storage conditions. When wet granulating is necessary for formulation, both the excipient and drug form may be altered. Subsequent interactions would differ from those of the original starting materials.

The economic considerations in terms of time and response, widely varying drug concentrations, multiple excipient interactions, processing variables and the dosage form make it evident that excipient testing is inefficient. A six-month compatibility study may easily cost $70,000 for sample preparation and analysis. Delay in bringing a valuable new drug to market is even more expensive. For a drug grossing $700 million per year, the figure is $2

million per day. If a competitor reaches market first, research efforts by the second developer could result in substantially reduced market share.

Important physical properties which can only be judged by formulation mandate the examination of authentic dosage forms. The apparent optimal formulation chosen after testing of binary mixtures may be impossible to make into a dosage form. A formulation that is chemically and physically stable that cannot be manufactured is useless.

ALTERNATIVE APPROACHES

Differential scanning calorimetry (DSC) and differential thermal analysis (DTA) frequently have been used for predicting incompatibilities between excipients and compounds, for example, with erythromycin[31], ampicillin[32], clembuterol[33], cephradine[34], nalidixic acid[35], cephalexin[31] and fenretinide[18]. In all of these reports powder mixtures of excipients and drug were used for the measurements. However, as is true with most reports on compatibilities, there has been no confirmation that these interactions have any significance with respect to the formulated product. In the report on fenretinide[18], it is stated that the DSC method was found to be an 'unreliable compatibility predictor for fenretinide'. This conclusion was reached with DSC results using dry powder mixtures and HPLC assays of single excipient-drug powder mixtures which were wetted and dried prior to storage at 25°C and 60°C. Of the six excipients tested, two were found to be incompatible using DSC but both were subsequently found to be compatible based on assay results after two months at 60°C and two years at 25°C. One excipient which was determined to be compatible using the DSC results actually caused significant degradation after exposure to 60°C for one month (33% reaction) or to 25°C for two years (29% reaction). How many more discrepancies would have been shown with respect to a formulated product indicating the worthlessness of excipient compatibility testing? However, DTA was shown to be useful in selecting a basic excipient as a solubilizer for cephradine[34] in a powder formulation.

Diffuse reflectance spectroscopy (DRS) has been used to study solid-solid compatibility. The technique has been used to detect drug degradation in the presence of excipient materials as well as physical and chemical adsorption of

excipient onto drug[17, 29]. Degradation has been detected by monitoring change in reflectance at a chosen wavelength on samples stored and analyzed over a period of weeks. As an analytical technique, DRS offers advantages of speed and simplicity. However, it lacks the specificity of stability-indicating HPLC methods. The determination of physical or chemical interactions between drug and excipient appears useful. However, correlations between such interactions and bioavailability have not been well established.

Radiolabeling has also been proposed[17] as a method of determining drug-excipient compatibility. The technique is sensitive, but cumbersome and expensive. Most stability-testing laboratories lack the equipment and the expertise to perform such analyses. Detection limits of many other methods are sufficient. Identification of degradation products is not possible with simple detection of radioactivity. Spectral detection methods offer much more information.

Rowe has proposed using solubility parameter maps as a predictor of compatibility between celluloses and plasticizers used in extended release formulations[36]. He has also used the technique to examine interactions of lubricants with microcrystalline cellulose and anhydrous lactose[37]. Non-isothermal stability testing has been investigated as a more rapid alternative to accelerated stability studies[38]. Samples are subjected to a linear increase in temperature, and the Arrhenius relationship is used to estimate their stability.

Measurements of drug binding to excipients have been included in compatibility studies. Even in vitro binding studies are of limited value in predicting bioavailability. Such results only have meaning if in vivo studies confirm whether the binding is significant with respect to pharmacodynamic or biopharmaceutical properties. The effect of drug-excipient interactions on drug absorption has been reviewed by Monkhouse and Lach[39]. The binding of ascorbic acid to silica gel has been shown to be a function of the moisture content[40], and bioassays showed bioavailability of ascorbic acid is unaffected by the presence of silica gel[41].

Drugs will bind to many excipients in artificial laboratory media; but under the conditions in the gastrointestinal tract, binding either does not occur

or the drug is rapidly and completely desorbed. For example, binding of oxymorphone derivatives to cross-linked carboxymethylcellulose sodium (Ac-Di-Sol) and sodium starch glycolate (Explotab) has been described with Freundlich adsorption isotherms[42]. A considerable amount of effort was expended on measuring the degree of binding at different concentrations and the effect of pH on binding. This interaction is, of course, one of ion exchange and should be predicted to occur for most basic drugs. However, it is of little or no consequence since in the ionic environment of the gastrointestinal tract the drug is rapidly and completely displaced. Binding of chlorpheniramine with cross-linked carboxymethylcellulose was shown by Fan[43]. He also found that dissolution of chlorpheniramine was complete in NaCl solution, dilute HCl and simulated gastric and intestinal fluids due to ion exchange. His conclusion was that 'the interaction between cationic drugs and cellulosic excipients should be expected to be inconsequential under normal physiological conditions'. This expectation was shown to be true for phenylpropanolamine HCl where no effect on bioavailability was seen for tablets containing cross-linked carboxymethylcellulose sodium (croscarmellose sodium) even though 40% of the phenylpropanolamine HCl was bound in water during a dissolution test[44]. Salicylic acid binds to magnesium oxide. This physical interaction in the solid state is observable by diffuse reflectance spectroscopy. However, the drug is easily removed by elution with water[29].

RECOMMENDATION AND RATIONALE

The theory of solid-state stability has been the subject of numerous publications[45-51]. Optimization of drug stability through dosage form design is a goal of many researchers[8, 11, 52-55]. Much information is available to aid in the design of dosage forms. After examining the preformulation data and structural features of the compound, the necessary excipients can be selected for initial formulation studies to impart the desired characteristics for formulation processing and dosage form performance.

The study of compaction properties has been recommended as part of a program of rational preformulation testing[56]. Using either intrumented tablet machines or compaction simulators, very little drug is required. Such

instrumentation should not be used solely to determine the compression characteristics of the drug[57,58]. Samples of actual target formulation(s) should be prepared. A stability-indicating assay is developed for the dosage form and applied to samples stored at elevated temperatures and humidities. If an instability is discovered, then the formulation components and the processing method must be examined to determine the reaction or physical mechanism.

Such mini-formulation studies are more efficient than excipient-compatibility testing. They yield more realistic information on dosage form stability, reduce drug consumption, and can decrease development time. Multiple interactions may be detected and sampling errors are reduced. Processing variables are best examined by preparation of authentic formulations. The importance of grinding, mixing, granulation and compaction in tablet manufacture is obvious. However, mini-formulation studies as described will be good predictors for capsules. Capsule formulations are not equivalent to loose powder mixes. Tamping effects[59], drug interactions with gelatin[60], and presence of moisture in the capsule shell all influence drug stability. A compact is a better predictor of both tablet and capsule formulation stability. Crystal characteristics affect both stability and tabletting behavior[20]. The most stable polymorph may not be most suitable for the manufacture of the formulated product, and processing frequently causes interconversions.

Although new and exotic materials are available for specialized applications, the bulk of new pharmaceutical products utilize only a handful of excipients[4]. Perhaps the most efficient means of dosage form development is the 'base formulation' approach. A series of premixed formulation bases should be designed and maintained on hand for the rapid preparation of prototype formulations. These bases should be well characterized, and that workup must include data on their interactions with acidic, basic and low-melting materials. The success of this method depends on knowledge of the chemistry of the drug substance and its behavior under compression. Use of a compaction simulator is invaluable in determining the latter. Such information would facilitate the choice of initial composition for a formulation.

As an adjunct to mini-formulation studies, drug-excipient compatibility testing is useful and should comprise part of the troubleshooting effort when prototype formulations have poor stability. On those odd occasions an abbreviated experiment would confirm the suspected cause of the instability.

CONCLUSION

The value of excipient compatibility testing as a preformulation tool has been overestimated. It is an empirical test which is too often used to make broad predictions. Its failure to detect incompatibilities has led to costly mistakes and delays in bringing new drugs to market. Its use should no longer be accepted without questioning. The goal of pharmaceutical development in an industrial setting is the timely introduction of a stable product. Optimal data are needed to make valid predictions. When compared to the conventional wisdom, mini-formulation studies may entail a small gamble. However, they constitute a sounder approach to the development of a stable dosage form.

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