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Investigation of stable storage condition for drug in the solid state-a Review

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Abstract: The primary objectives of this investigation are identification of stable storage conditions for drug in the solid state and identification of compatible excipients for a formulation. Contrary to the earlier solution stability profile, these solid-state studies may be severely affected by changes in purity and crystallinity, which often result from process improvements. Repetitive besting of the initial bulk lot in parallel with newer bulk lots should be expected, and adequate material should be set aside for these studies.

Key words: solid state, stability, purity, crystallinity, bulk, adequate material.

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1. Introduction: In general, solid state reactions are much slower and more difficult to interpret than solution state contacts between drug and excipient molecules and to the occurrence of multiple-phase reactions. A kinetic analysis of slow solid-state degradation based on retention of intact drug may fail to quantitate clearly the compound's shelf-life, as

assay variation may equal or exceed the limited apparent degradation, particularly at the low temperatures that are critical to establishing a room-temperature shelf-life. Usually, this situation may be corrected on analysis of the appearances of decay product(s), which may total only 1 to 5% of the sample. Additional analytic data from such studies as TLC, fluorescence, or UV/VIS spectroscopy may be required to determine precisely the kinetics of decay product(s) appearance, and to establish a room-temperature shelf-life for the drug candidate.

2. Literature overview:

1. A review on pharmaceutical pre-formulation studies in formulation and development of new drug molecules – by GitaChaurasia.
2. Analytical techniques in pharmaceutical analysis: a review – by MasoomRazaSiddiqui, Jeid A Alothman, NafisurRahman.
3. Review – Temperature excursion management: A Novel approach of quality system in pharmaceutical industry – by Nirmal Kumar, AjeyaJha.
4. Solid state amorphization of rebemipide and investigation of solubility and stability of amorphous form – by XinnuoXiong, KailinXu, Shanshan Li, et al.
5. Pre-formulation studies of drug substance for solid dosage form – by HarkanNyqvist.
6. A review on polymorphism perpetuates pharmaceuticals – by Nalliboyina. LakshmiPrasanthi, M. Sudhir.
7. Drug excipient interaction in the solid state: The role of different stress factor – by CarinnaGressl, Adrian Dais, et al.

3. Experimental review: To study the many possible solid-state reactions, one may need more than a specific assay for the intact compound. Polymorphic changes, for example, are usually detected by differential scanning calorimetry or quantitative infrared analysis (IR). In the case of surface discoloration due to oxidation or reaction with excipients, surface reflectance equipment may be more sensitive than HPLC assay. In any event, additional samples to accommodate these additional tests.

To determine the solid-state stability profile of a new compound, weighed samples are placed in open screw cap vials and are exposed directly to a variety of temperatures, humidities, and light intensities for up to 12 weeks. Samples usually consists of three 5- to 10- mg weighed samples at each data point for HPLC analysis and approximately 10 to 50 mg of sample for polymorph evaluation by DSC and IR (~2 mg in KBr

and ~20 mg in Nujol). To test for surface oxidation, samples are stored in large (25-ml) vials for injection capped with a Teflon- linked rubber stopper and the headspace flooded with dry oxygen. To confirm that the decay observed is due solely to oxygen rather than to reduced humidity, a second set of vials should be tested in which the atmosphere is flooded with dry nitrogen. After a fixed exposure time, these samples are removed and analyzed by multiple methods to check for chemical stability, polymorphic changes, and discoloration.

Once the results of this initial screen are tabulated, the decay process may be analyzed by either zero-order or first-order kinetics, particularly if the amount of decay is less than 15 to 20%. The same kinetic order should be used to analyzed the data at each temperature if possible. Samples exposed to oxygen, light, and humidity may suggest the need for a followup stability test at three or more levels of a given parameter for full quantitation of its involvement.

In the event that humidity is not a factor in drug stability, an Arrhenius plot may be constructed; if linear, it may be extrapolated to "use" conditions for predicting a shelf-life. If humidity directly affects drug stability, the concentration of water in the atmosphere may be determined from the relative humidity and temperature by using psychrometriccharts[1]. Stability data obtained at various humidities may be linearized with respect to moisture using the following apparent decay rate constant:

$K_H = [gpl]. K_0$

Where [gpl] is the concentration of water in the atmosphere in units of grams of water per liter of dry air, and k_0 is the decay rate constant at zero relative humidity. For example, a 75% relative humidity atmosphere at 37^0C is equivalent to 0.0405 grams of water per liter (gpl) of dry air. When the effect of moisture on chemical stability is examined in details, a comparison to solution state stability and hygroscopicity data may suggest an aqueous reaction occurring in the drug-saturated water layer on the crystal surface.

Another useful relationship for analyzing solid state stability data assumes that a compound must partially liquefy prior to decomposition. Given that the mole fraction of the solid that has liquefied (F_m) is directly proportional to its decay rate[2], then:

$\ln K_{app} \alpha \ln F_m = [\ -\ ]$

WhereΔH_{fus} is the molar heat of fusion, Tm is the absolute melting point (^{0}kelvin), T is the absolute temperature of the stability study, and R is the gas constant.

Once bulk drug stability has been determined, compatibility with excipients commonly used to produce solid dosage forms must be established.According to the stabily profile of the earlier solution the solid state studies are affected by several changes in purity and crystallinity[3]. The number of excipients may be reduced by considering the results of the solid state and solution stability profiles. For examples, a compound with bulk instability at high humidity should be formulated with anhydrous excipients. Similarly, the pH of maximum drug stability should match the pH of an aqueous suspension and solution of the drug and excipients.

When a reduced number of molecular contacts between drug and exicipient molecules ossurs then the solid state reactions are much slower and more difficult to interpret;thus the multiple phase reactions occurs.[4][5].

4. Some uses as: A list of most common excipients created along with hypothetic formulation utilizing these excipients.

Usually the approximate dose of drug is known; Eachexcipient can be blend with drug at levels that are realistic with respect to final dosage form. Each blend is then divided into weighed aliquots, which are tested for stability at high temperature lower than the melting point of the ingredients.

Pellets should be formed from the drug excipient blends to increase drug-excipient contact and accelerate testing.

5. Conclusion: Excipients compatibility testing for small batches – Hypothetic capsule or tablet formulation should be prepare and tested in same stability protocol to check the incompatibility arising from a multi component formulation. Solid formulation often required granulation of the drug excipient blend to improve flow, density, homogeneity. Stability during the granulation process may be checked by excessive weight drying at samples of the unformulated bulk, excipient drug blends and the hypothetic formulation. This wet-downs should utilize only pharmaceutically acceptable solvent with or without such approve

binders as methyl cellulose and PVP. After checking the crystallinity, polymorphism and solvate formation solid state stability can be checked.

6. References:

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