"Drug Stability and factors that affect on the drug stability"

Review BY

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Abstract:

Evaluation of the stability of drugs and drug metabolites in a biological matrix is a critical element to bio analytical method validation. It is critical to understand the most common factors that affect the stability of such analytes in order to properly develop methods for their detection and measurement. The degradation of drugs and drug metabolites in samples can occur through either reversible or irreversible processes. Common factors that affect this stability include temperature, light, pH, oxidation and enzymatic degradation. Special considerations are also required when dealing with chiral molecules, deuterated internal standards and large biomolecules. Relevant examples of these degradation effects and approaches for dealing with them are presented is this review as taken from the fields of pharmaceutical testing, clinical research and forensic analysis. It is demonstrated through these examples how an understanding of the chemical and physical factors that affect sample stability can be used to avoid stability problems and to create robust and accurate methods for the analysis of drugs and related compounds.

INTRODUCTION:

Drug stability means the ability of the pharmaceutical dosage form to maintain the physical, chemical, therapeutic and microbial properties during the time of storage and usage by the patient. It is measured by the rate of changes that take place in the pharmaceutical dosage forms. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light, and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions. Although the pharmaceutical scientist plays a critical role in determining the stability of pharmaceuticals, practicing pharmacists should be able to interpret this information for their patients. This chapter introduces the rates and mechanisms of reactions with particular emphasis on decomposition and stabilization of drug products. It is essential for pharmacists and pharmaceutical scientists to study, understand, and interpret conditions of instability of pharmaceutical products as well as to be able to offer solutions for the stabilization of these products.

Factors affecting drug stability:

There are many factors that affecting such as temperature so high temperature accelerate oxidation, reduction and hydrolysis reaction which lead to drug degradation and the pH in which the acidic and alkaline pH influence the rate of decomposition of most drugs. and many drugs are stable between pH 4 and 8.

The Weekly acidic and basic drugs shows good solubility when they are ionized and they also decompose faster when they are ionized. So if the pH of a drug solution has to be adjusted to improve solubility and the resultant pH leads to instability then a way out of this tricky problem is to introduce a water-miscible solvent into the product. It will increase stability by: suppressing ionization reducing the extreme pH required to achieve solubility enhancing solubility - reducing the water activity by reducing the polarity of the solvent. For example, 20% propylene glycol is placed in chlordiazepoxide injection for this purpose.

The Reactions catalyzed by pH are monitored by measuring degradation rates against pH, keeping temperature, ionic strength and solvent concentration constant. Some buffers such as acetate, citrate, lactate, phosphate and ascorbate buffers are utilized to prevent drastic change in pH. Sometimes pH can have a very serious effect on decomposition. As little as 1 pH unit change in pH can cause a change of ten fold in rate constant. So when we are formulating a drug into a solution we should carefully prepare a pH decomposition profile and then formulate the solution at a pH which is acceptable physiologically and stability-wise also.The third one is moisture in which the water catalysis chemical reactions as oxidation, hydrolysis and reduction reaction and the water promotes microbial growth as well as Light affects drug stability through its energy or thermal effect which lead to oxidation and Pharmaceutical dosage forms: solid dosage forms are more stable than liquid dosage forms for presence of water while the concentration: rate of drug degradation is constant for the solutions of the same drug with different concentration. So, ratio of degraded part to total amount of drug in diluted solution is bigger than of concentrated solution. Stock

solutions: are concentrated solutions which diluted by using (i.e. syrup 85%) at high concentration the stability is high and the drug incompatibility: reactions between components of pharmaceutical dosage forms itself or between these components and cover of the container while the Oxygen: exposure of drug formulations to oxygen affects their stability.

• **Three stabilities of drug must be considered:**

Frist of all is Physical stability. Secondly is chemical stability and microbiological stability Physical stability. Physical instabilities possibilities are: Crystal formation in pharmaceutical preparations Causes: a. Polymorphism phenomena: i.e. Chloramphenicol (change of amorphous to crystalline form. b. Saturated solution: by different temperature precipitation of solute may occur. C. In suspension: when very fine powder is used a part of suspending agent will dissolve then precipitate as crystal. Loss of volatile substances from pharmaceutical dosage forms: Examples: a. Aromatic waters b. Elixirs c. Spirits d. Some types of tablets which contain aromatic water (Nitroglycerin tablets) and Loss of water: This can be seen in the following dosage forms: a. saturated solution: by loss of water they become supersaturated and precipitate as crystals is formed b.Emulsions: Loss of water lead to separation of the two phases and change to other type c. Creams: especially oil/water, they become dry by loss of water d. Pastes e. Ointments: especially aqueous base ointments Humectants is added to the previous dosage forms which defined as hydrophilic substances added to aqueous phase to absorb water from atmosphere and prevent its loss from the dosage forms. Examples: Glycerin and Absorption of water: This phenomena can be seen in the following pharmaceutical forms: a. Liquefaction and

degradation may occur as a result of absorption of water b. Suppositories which base made from hydrophilic substances as Glycerin, Gelatin, and poly ethylene glycol. The consistency of these forms becomes jelly-like appearance and change in crystalline form: Example: Cocoa butter which is capable of existing in four polymorphic forms.

Chemical stability

Solid state reactions are generally slow and it is customary to use stress conditions in investigation of stability and data obtained under stress is then extrapolated to make prediction of stability. High temperature can drive moisture out of a sample and render the material apparently stable otherwise prone to hydrolysis. i.e. above 65% relative humidity the beta form of chlortetracycline hydrochloride transforms into alpha form.

Functional group undergoing oxidation	Resulting oxidation product	Example drugs
Phenolic OH, catechols	Carbonyl group	Propofol, epinephrine and related catecholamines
Phenolic OH	Dimeric product	Morphine
Amine	N-oxide	Morphine
Thioether	S-oxide	Promethazine and related phenothiazines
Thiol	Disulphide	Captopril, 6-Mercaptopurine
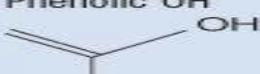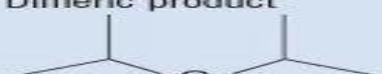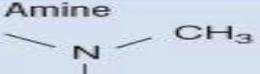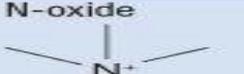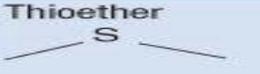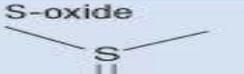
Microbiological stability:

Contamination from microorganisms is a big problem for all formulations containing moisture but it can be a bother in solid dosage forms also if some natural polymers are used because many Natural polymers are fertile sources of microorganisms. In the type of hygienic manufacture carried out today where Quality Assurance is a prerequisite as per the GMP procedures, there are definite procedures to prevent microbial contamination in all formulations. Sources of Microbial Contamination: Water, Air, Raw materials, containers and closures, Personnel and Instruments and apparatus.

Sources of microbial contaminations

Water	Low demand gram-negative groups: Pseudomonas, Xanthamonas, Flavobacterium, Achromobacter
Air	Mould spores: Penicillium, Mucor, Aspergillus Bacterial spores: Bacillus spp. Yeasts
Raw Materials	Micrococci
Earths	Anaerobic spore formers: Clostridium spp
Pigments	Salmonella
Starches	Coliforms
Gums	Actinomyces
Animal products	Salmonella, Coliforms
Personnel	Coliforms, Staphylococci, Sterptococci, Coryembacteria

Effect of light

Many drugs fade or darken on exposure to light and this leads to an aesthetic problem. Real photochemical reactions, photochemical catalytic reactions and Photochemical sensibilized reactions

Effect of packaging

Material, Glass, Plastics, Metal, Rubber Glass Glass is resistant to chemical and physical change and is the most commonly used material. is resistant to chemical and physical change and is the most commonly used material.

Plastics

The problems with plastic are: 1. Migration of the drug through the plastic into the environment. 2. Transfer of environmental moisture, oxygen, and other elements into the pharmaceutical product. 3. Leaching of container ingredients into the drug. 4. Adsorption of the active drug or excipients by the plastic.

Metals

Various alloys and aluminum tubes may be utilized as containers for emulsions, ointments, creams and pastes. Limitation: They may cause corrosion and precipitation in the drug product. Overcome: Coating the tubes with polymers may reduce these tendencies.

Rubber

Rubber also has the problems of extraction of drug ingredients and leaching of container ingredients. The pretreatment of rubber vial stoppers and closures with water and steam reduces potential leaching.

The instability possibilities in different formulations

Oral solutions Instability problems. Loss of flavor, Change in taste, Presence of off flavors due to interaction with plastic bottle, Loss of dye, Precipitation, Discoloration Effects. Change in smell or feel or taste Steps to prevent instability: Use of proper excipients and suitable packing materials. Parenteral solutions physical instability occurs due to: Interact contents with the container, Changes in Chemical composition. Instability problems, Discoloration due to photo chemical reaction or oxidation. Ex: thiamine hydrochloride Presence of precipitate due to interaction with container or stopper. Presence of "whiskers". If some small pinholes are present in the ampule due to improper sealing the solution wicks out, the liquid evaporates and the solid settles on the outside. It further helps in wicking out more solution and long lines of crystals form on the outside of the vial which are called whiskers. This may happen due too small hole (<0.5 µm) going undetected or the crack developing during storage. Clouds: A cloud will appear in the product due to: Chemical changes an ester eg.a polysorbate may hydrolyse producing an acid which is poorly soluble) b.Solubility product may be exceeded. c.The original preparation of a supersaturated solution or the use of a metastable form (ex: calcium gluceptate). Effects: Change in appearance and in bioavailability. Steps to prevent instability: 1.Use of antioxidants (0.5%) Acetylcystane or 0.02 – 1% Ascorbic acid) or Chelating agents (0.01 – 0.075 sodium edetate) to prevent discoloration. 2. Change in stopper or material of the container will eliminate the problem. 3.Checking of the

manufacturing process Increasing solubility by the use of co solvents (eg: polyethylene glycol) or by other methods such as micellar approach or complexation will reduce clouding.3))Suspensions This instability occurs due to: a. Particle diameter b. Concentration of suspending agent c. Viscosity of surrounded media d. Temperature e. pH f. Presence of microbes Instability problems 1,Settling ,Caking 3.Crystal growth Effects: Loss of drug content uniformity in different doses from the bottle and loss of elegance.

Steps to prevent instability:
 Design of product based on proper pre-formulation studies.
 Emulsions
This instability occurs due to: a. Droplet diameter b. Viscosity c. Difference in Density d. Temperature e. pH f. Presence of microbes Instability problems 1.Creaming 2.Cracking Effects: Loss of drug content uniformity in different doses from the bottle and loss of elegance.

5. Semisolids (Ointments and suppositories) Instability problems
1. Changes in: a .Particle size b. Polymorphic state, or hydration or solvation state c. Consistency d. drug release rate 2.Caking or coalescence. 3. Bleeding. Effects: Loss of drug content uniformity, loss of elegance and change in drug release rate.

6. Tablets
Instability problems Change in: a. Disintegration time b. Dissolution profile c. Hardness d. Appearance Effects: Change in drug release

7. Capsules

Instability problems Change in a. Appearance b. Dissolution c. Strength Effects: Change in drug release

SUMMARY

Drug Stability is important to be studied for the sake of patient's welfare to warrant safety, quality and efficacy of medication Modes of instability of drugs including chemical, physical, microbiological, therapeutic, toxic degradation Can be done for bulk drug substance and excipients, R&D Formulations, Marketed products, Clinical Trial Materials etc Potential adverse effect of instability including loss/increase in concentration of active, alterations of BA, loss of content uniformity, decline of microbiological status etc

References

1. Vigneron J. Stability: Ten pieces of advice. EJHP Science 2008; 14:2.
2. Allwood M. Assessing the shelf life of aseptically prepared injectabilies in ready to administer containers. Eur J Hosp Pharm 2012; 19:277.
3. Bardin C, Astier A, Vulto A, et al. Guidelines for the practical stability studies of anticancer drugs: a European consensus conference. Eur J Hosp Pharm 2012; 19:278–85.
4. Carati D, Masini C, Minguzzi M, et al. Stability of bortezomib reconstituted under clinical conditions in original vials and polypropylene syringes at 4°C and room temperature. Eur J Hosp Pharm 2012; 19:428–31.
5. Helin-Tanninen M, Autio K, Keski-Rahkonen P, et al. Comparison of six different suspension vehicles in compounding of oral extemporeous nifedipine suspension for paediatric patients. Eur J Hosp Pharm.