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SHORT COMMUNICATION

STABILITY OF PHARMACEUTICAL FORMULATIONS

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Pharmaceutical formulation is the means whereby a drug is converted into a medicine, that is, to a suitable form for administration to a patient by a particular route. The object is to produce a medicine, in a suitable package, that possesses the following desirable properties.

— bioavailability and efficacy acceptability
—convenience for use
—stability over prolonged storage.

The conversion of a drug into a medicine often involves the addition of pharmaceutical adjuvants (excipients) such as binding agents, disintegrating agents, antioxidants, antimicrobial preservative and emulsifying agents etc. The stability of a medicine relates to the various changes that may occur in the medicine during preparation and storage and to the impact of those changes on its fitness for use.

Most medicines are complex physico-chemical systems, and are subject to deterioration by a variety of chemical, physical, and microbial reactions; interaction between the drug, adjuvants, container and closure may occur and this may either lead to the inactivation of the drug through decomposition or loss of the drug by its conversion to a less favourable physical or chemical form. Deterioration is released by the change that occur, but not always, such as alteration in colour, odour, viscosity, precipitation, phase separation, cracking and caking and also leakages due to mechanical hazard of handling or transport, which can be readily detected by the senses.

Degradation during storage and transportation is of particular importance in tropical countries. Indeed, an expiry date determined for a temperate climate may be inappropriate in a tropical region even when high standards of packaging are met. For this reason, particular importance is accorded to visual inspection of dosage forms, since this frequently provides a first vital indication of degradation which may be due to poor manufacture, tampering or counterfeiting.

No pharmaceutical product is stable indefinitely and certainly the majority of products are stable only for a limited time. The instability may be demonstrated as drug or excipients degradation. Instability is thermodynamic in nature, but this may further

aggravate by poor formulation, poor packaging and poor storage conditions. Some of the six possible result of pharmaceutical product instability are:

1. Loss of active drug (e.g. aspirin hydrolysis, oxidation of adrenaline).
2. Loss of vehicle (e.g. evaporation of water from o/w creams, evaporation of alcohol from alcoholic mixtures).
3. Loss of content uniformity (e.g. creaming of emulsions, impaction of suspensions).
4. Loss of elegance (e.g. fading of tablets and coloured solutions).
5. Reduction in bioavailability (e.g. ageng of tablets resulting in a change in dissolution profile).
6. Production of potential toxic materials (e.g. breakdown products from drug degradation).

Stability is often expressed as *shelf-life,* that is, the period of time that a medicine is expected to retain its potency and efficacy and remain fit for use, from the preparation of the product until the potency or content of the drug is reduced by a acceptable limit (10%), under specified storage conditions or stored at room temperature (25°C) in warehouse or pharmacy. The limit of 10% is usually considered to be acceptable in practice although more stringent measures are required to be taken specially for drugs with poor stability (mixtures etc.), as the degradation products could be more toxic and irritant than the drug. Although it is convenient to express the shelf-life of a drug soley in terms of the chemical stability of its active ingredient, it is important that other desirable properties of the medicines are maintained and are taken care of during storage.

The chemical aspects of formulation generally centre around the chemical stability of the drug and its compatibility with other formulation ingredients. Drugs and adjuvants may degrade by various chemical reactions. Since chemical reactions proceed more rapidly in the liquid state than in the solid state, solid medicines are usually more stable than the liquid medicines; the stability of suspension of solids in liquid is generally greater than that of the solutions. The degradation may be due to physical, chemical or biological mechanism. In some cases the degradation may be due to one or more of these mechanisms or what appears to be the result of one mechanism may be the result of another mechanism e.g. cracked emulsion (a physical effect) may be the result of microbial degradation of emulsifier.

The most common reactions influencing chemical degradation are oxidation, hydrolysis and photolysis, while factors affecting physical degradation may be due to pH, temperature, light, carbon dioxide and humidity etc.

Oxidation is an extremely common cause of drug and excipients degradation. The degradation may occur in both water- and oil- soluble drugs, as well as in fired and volatile oils. Two types of oxidation processes affect pharmaceuticals i.e. those involving atmospheric oxygen, also referred to as autoxidation and those involving the reversible

loss of electrons. Autoxidation is often catalysed by light and trace metals. Oxidised solutions are often coloured. The oxidation of some substances (e.g. ascorbic acid) in aqueous solution may be reversible (redox) reactions that involve the loss of electrons without the addition of oxygen. Oxidation of some drugs in aqueous solution may be reduced by lowering the pH to between 3 and 4. Oxidation can also be retarded by the use of antioxidants. Where the rate of drug degradation is significantly relative to that of the antioxidant, it may be necessary to exclude oxygen by flushing the preparation with nitrogen.

Hydrolysis is another important cause of degradation, as in most pharmaceutical formulations the solvent is water and unfortunately many ester and amide drugs hydrolyse in water (e.g. hydrolysis of aspirin and sulphacetamide). However, in some pharmaceutical products the solvent may include such co-solvents as ethyl alcohol, propylene glycol and glycerol together with water. The rate of hydrolysis may vary depending on the pH of the solution, thus drug degradation due to hydrolysis may be reduced by preparation of solution at the pH at which hydrolysis is minimised. If the pH for maximum stability of the drug cannot be tolerated physiologically or if the degradation rate of another constituent of the medicine is too great at the pH, the solution may have to be buffered at a pH at which the stability is only just acceptable. In complex formulations, such as vitamins, a compromising pH has to be found, at which all the individual constituents could exhibit maximum possible stability.

Photolysis is *yet* another factor causing drug degradation. Light, either room light or sunlight may causes degradation of the drug or excipient molecule. The shorter the wavelength the more potentially damaging is the light. Thus UV light is more harmful than the visible light and hastens photochemical reaction. However,in order to initiate a photolytic reaction the energy from the light radiation must be absorbed by the molecules. If the energy absorbed is sufficient to achieve the activation energy, then degradation of the molecule is possible. In certain cases, the molecules absorbing the light pass on their increased energy to other molecules which then degrade (photosensitization). Since the light energy may be converted to heat, photolysis may be accompanied by a thermal reaction. Photolytic reactions include the decomposition of riboflavin and chlorpromazine HUI, the darkening of morphine and codeine, the fading of tatrazine dye etc. Photochemical degradation can be prevented by the use of amber or other light-resistant containers or, more efficectively, by storage of the product in the dark.

The stability of pharmaceutical formulations under different conditions of vehicle, pH, buffer kind and concentration eta may be conveniently evaluated by accelerated storage testing using stability-inrlirating analytical methods. The method involves the accelerated breakdown of a drug in the proposed medium at elevated temperatures and determining the rates of degradation to predict the shelf-life at room temperature.

Dosage form also plays a most important role in the stability of a formulation be-

sides good quality compatible packaging material. The packaging should be so designed that the chemical integrity of drug substance is maintained during usable life of the product and that it should not react with the medicine. The formulation and associated preparation of dosage forms demand careful examination, analysis and evaluation of wide ranging information. The manufacturer must ensure that the drug he produces is sufficiently stable and that it can be stored for reasonable length of time without changing to a less active, inactive or toxic form; the pharmacist must be fully aware of the potential instability of the drug and the chemical nature of the sub-stance that are being handled so that the possible type and cause of degradation can be assessed and suitable measures taken to retard the reaction; and the physician and patient must be assured that the drug prescribed will eventually reach its locus of action in sufficient concentration to elicit the desired effect. All these measures are aimed to achieve the objective of creating high quality, safe and efficacious stable dosage forms.

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