Criteria for Judging the Quality of a Publication on Physicochemical Stability of Ready to Use Injectable Drugs

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Review

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Abstract: In hospitals, a major part of the drugs is administered via the intravenous route. When one wants to evaluate or know the stability of a drug in solution, it is necessary to know several physico-chemical parameters. Several reference works are available to help the hospital pharmacist with this research. However, reading these different sources can make you discover conflicting data. It is therefore necessary at this time to obtain the publications with contradictory results and to read them again. Seven criteria have been identified for judging the quality of a publication on physicochemical stability: full description of equipment, methods and analytical conditions of molecules studied; complete description of the procedures used to validate the analytical method; full indication of time testing and measurement bases or control; documentation on the analytical reproducibility; adequate statistical analysis; appropriate conclusions; appropriate references. In conclusion, everything in a compatibility study is important.

Keywords: physico-chemical stability, injectable drugs, drug stability, CIVAS

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Introduction

In hospitals, a major part of the drugs is administered via the intravenous route. Several authors tried to quantify the quantity of injectables administered to the patients.

Turco SJ [1] reports that 24 % of the administered doses in the hospital are injectable drugs, just as 38 % of the patients receive at least an injection per day.

According to Simons BP [2], 30 to 50 % of the patients receive medications via the intravenous route, a percentage confirmed by Taxis K (28 %), Bernaerts K (34 %) and Champion K (23 to 25 %) [3–5].

Kwan JW [6] estimates that 40 % of medications and solutions are administered via the intravenous route while Rwabihama JP [7] notes that 49 % of the patients are under perfusion.

Recently, Fekadu et al reported that 50 %, 32.1 % and 12.7 % of patients receive two, three or four intravenous drugs per prescription, respectively [8].

When one wants to evaluate or know the stability of a drug in solution, it is necessary to know: final concentration of the reconstituted product, nature, pH and ionic force of the diluent, pH and ionic force of final dilution, nature of the container (polyvinyl chloride (PVC), ethylvinyl acetate (EVA), polypropylene, ...) to avoid the phenomenon of sorption and salting out, conditions of storage (refrigerator, ambient temperature, body temperature, protection from light), nature of the set of administration (PVC, polyethylene, ...), protection from light during the administration [9].

Which healthcare professional may answer to these questions? Hasegawa gives the response in 1994: “Caring about stability and compatibility may not excite many pharmacists. However, no other health professionals are as qualified or as obligated to effectively apply their training and experience and the abundance of published data to this aspect of patient care” [10].

Several reference works are available to help the hospital pharmacist with this research [11–19] and have been evaluated [20].

However, reading these different sources can make you discover conflicting data.

It is therefore necessary at this time to obtain the publications with contradictory results and to read them again.

Guidelines are available to perform stability studies [21]. However, they have been designed for purposes not entirely covering the practical needs [22].). Indeed, ICH guidelines have the objective to regulate the quality of marketed drugs in an international context and pharmacopeia monographs often refer to raw materials and offer no solution when applied to marketed products under practical conditions [22].

Some papers have been published to approach field practice [22–25].

Criteria for judging the quality of a publication on physicochemical stability

A review of the literature on this subject identified some papers written by different authors, and seven criteria have been identified: full description of equipment, methods and analytical conditions of molecules studied; complete description of the procedures used to validate the analytical method; full indication of time testing and measurement bases or control; documentation on the analytical reproducibility; adequate statistical analysis; appropriate conclusions; appropriate references [26–34]

Description of the preparation and storage of the ready to use or ready to administer drugs

The following information must be specified: complete drug formulation, manufacturer and batch number of the molecules, the solutions and the containers.

Indeed, similar products from different suppliers may have differing formulations that can affect results.

The method of reconstitution must be described, with the conditions of environment: under laminar air flow cabinet or isolator, under clinical conditions, in the ward area etc.

Full description of equipment, methods and analytical conditions of molecules studied

High performance liquid chromatography (HPLC) is the most important used method. Alternatives are capillary electrophoresis and high performance thin layer chromatography [23].

The following information must be specified: manufacturer and batch number of the chemicals, identification of equipment and devices, of other equipment used for the analysis (pH meter, microscope, spectrophotometer etc.). Solution preparations, standard solutions, quality-control solutions, chromatographic conditions, pH determination must also be specified, ideally in separate subtitles, to permit the replication of the study.

The temperature of storage must be specified: deep freezing: < - 15 °C; refrigerator: 2 to 8 °C, cool temperature: 8 to 15 °C, room temperature: 15 to 25 °C.

To increase their period of validity, some drug solutions are frozen. The method of thawing must be described with precision: room temperature, bags in a laminar flow to a constant renewal of the air at the surface of the bag, water bath, forced ventilation air fan, microwave oven [35].

If only the words “room temperature” are specified, the reader will refer to the country and the climatic zone in which the study was carried out.

The World Health Organization has defined 5 climatic zones and respective climatic conditions [36]. Mean annual temperature can vary from 20 °C (Zone I) to 26.7 °C (Zone IV). The temperature of use may also be described: room temperature, skin temperature (30 to 32 °C), body temperature (36.1 to 37.8 °C).

If the pharmacist has a climate chamber, stability testing is performed at 25 °C while maintaining the residual moisture at 60 ± 5 %, in order to achieve the conditions recommended by the ICH [21]. Otherwise, the study will be conducted under local residual moisture conditions, and it is recommended that measurement is taken regularly ([23].

The duration of the drug administration is also important for the duration of the physico-chemical stability.

Most products are exposed to light, particularly during prolonged administration regimens. Ensuring that the product is stable when exposed to light is an imperative condition, especially for products known to be light-sensitive. Storing samples in an open laboratory environment, subject to diffuse daylight and fluorescent room lighting will detect any serious light stability problems. Comparisons should be made to control samples, stored at the same time but protected from light [37].

Intravenous drug solutions are stored in plastic containers. The term “plastic” is not sufficiently precise. The European Pharmacopeia gives a full description of the

different plastics: polyolefines, polyethylene without additives for containers for preparations for parenteral and for ophthalmic preparations, polyethylene with additives for containers for preparations for parenteral and for ophthalmic preparations, polypropylene for containers and closures for parenteral and ophthalmic preparations, poly(ethylene–vinylacetate) for containers and tubing for total parenteral nutrition preparations, silicone oil used as a lubricant, silicone elastomer for closures and tubing, plastic additives, materials based on plasticized PVC for containers for aqueous solutions for IV-infusion [38].

Complete description of the procedures used to validate the analytical method

This section must include documentation which confirms that the analytical method is "stability indicating": validation of HPLC method and stability indication; the HPLC assay must be described and illustrated: calibration curve, chromatograms, calculations (references of the software).

It must be demonstrated that the method can distinguish between the parent substance and its degradation products, but also any other products present in the solution.

A stability indicating-assay is a validated quantitative analytical method that can detect the changes over time in the chemical or physical properties of the drug substance, and that are specific so that active ingredient, degradation products, and other components of interest can be accurately distinguished without interference. The assay must establish that there is no interference of the assay by vehicles or degradation by-products and usually involves forced degradation of the parent chemical to determine the nature and chromatographic peak of degradation by-products and other excipients.

The validation of an analytical method can involve the analysis of several parameters such as the specificity, precision, accuracy etc.: the specificity is the degree to which the method can quantify the analyte of interest accurately in presence of components which may be expected to be present. The accuracy expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found, and the precision specifies the closeness of agreement between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. The precision includes the within (same conditions of measurements) and between (variation in conditions among runs) days reproducibility. The precision is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements.

The presence of particles has to be searched by microscopic analysis with a detection level of 500 nm, currently used for the medical particles measurement [38].

Documentation on the analytical reproducibility

Investigators should provide documentation indicating the reproducibility of their method to ensure that their method can easily discern the slightest change in concentration.

Full indication of time testing and measurement bases or control

The publication must mention full indication of time testing and measurement bases or control.

If an initial measurement (time zero) is not reported in the stability study, the conclusions concerning the stability of the compound cannot be made with confidence.

Biological products like monoclonal antibodies constitute a special case. Because of their protein nature, these molecules may go through a variety of chemical and degradation processes. The long term stability of reconstituted drugs must be certified by several analyses as, for example, turbidimetric determination by UV-VIS spectrophotometry, tertiary structure analysis by second derivative UV spectroscopy, determination of molecular hydrodynamic diameters by dynamic light scattering (DLS), thermal denaturation curves by DLS, secondary structure analysis by second derivative FR-IR spectroscopy, chromatographic analysis (cation exchange chromatography, size-exclusion chromatography etc.) [39–44]

Adequate statistical analysis

In the absence of toxic degradation products, or physical changes, the end of a product's shelf life is often assumed as when the content reaches 90 % of the label claim. The best approach to analyze all the data points is based upon regression analysis. For most drugs, the degradation follows a first-order kinetic. As recommended by the Food and Drug Administration, it is classical to base the expiry time on the one-sided lower 95 % confidence limit of the regression line [45]. However, this view is now challenged by some authors [46].

Appropriate conclusions

The conclusions should reflect the overall results observed in the document and must be in accordance with these results.

A drug solution cannot be certified "stable" if physical stability and chemical stability have not been studied jointly: these two types of stability are complementary; a physically stable product is not necessary chemically stable and vice versa.

The observed results cannot be extrapolated ipso facto to other storage conditions not studied in the publication.

The Stabilis database [18] has recently been enriched with a rating grid for anticancer molecules. The scale is "A" (visual inspection, HPLC with diode array detector with over 95 % initial concentration, measured pH and no degradation product observed under actual conditions() to D (established stability with 90 % of initial concentration but separative method with one or more failing criteria OR stability established with 95 % of the initial concentration but separative method with more than 2 criteria failing OR unjustified choice of a method other than HPLC and stability established with 90 % of initial concentration).

Appropriate references

Before starting their study, the authors made sure that it had not already been carried out by another research team, by a review of the literature. This review of the literature will be included in the references and commented in the discussion. This review should be as exhaustive as possible and contain the original publications and not only the comments of these original publications.

Conclusion

This review of criteria should help the reader to judge a publication of physico-chemical stability.

Some databases also show a level of proof by stability study and, to use the title of two publications by L Trissel, "Everything in a compatibility study is important" and "Don't ignore details of drug-compatibility reports". If they are not very recent, they nevertheless remain current.

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