European Journal of Pharmaceutics and Biopharmaceutics 98 (2016) 26–46

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Review Article

Forced degradation studies of biopharmaceuticals: Selection of stress conditions

Elnaz Tamizi [a], Abolghasem Jouyban [b,*]

[a] Drug Applied Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Pharmaceutical Analysis Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

ARTICLE INFO

Article history:
Received 30 June 2015
Revised 21 October 2015
Accepted in revised form 28 October 2015
Available online 2 November 2015

Keywords:
Biopharmaceutical
Forced degradation
Stability
Stress condition
Stress testing

ABSTRACT

Stability studies under stress conditions or forced degradation studies play an important role in different phases of development and production of biopharmaceuticals and biological products. These studies are mostly applicable to selection of suitable candidates and formulation developments, comparability studies, elucidation of possible degradation pathways and identification of degradation products, as well as, development of stability indicating methods. Despite the integral part of these studies in biopharmaceutical industry, there is no well-established protocol for the selection of stress conditions, timing of stress testing and required extent of degradation. Therefore, due to the present gap in the stability studies guidelines, it is the responsibility of researchers working in academia and biopharmaceutical industry to set up forced degradation experiments that could fulfill all the expectations from the stability studies of biopharmaceuticals under stress conditions. Concerning the importance of the function of desired stress conditions in forced degradation studies, the present review aims to provide a practical summary of the applicable stress conditions in forced degradation studies of biopharmaceuticals according to the papers published in a time period of 1992–2015 giving detailed information about the experimental conditions utilized to induce required stresses.

© 2015 Elsevier B.V. All rights reserved.

1. Introduction

Owing to the extreme improvements in protein chemistry and modern biotechnological procedures such as DNA recombinant and hybridoma technologies, development and production of biopharmaceuticals have turned to be the fastest growing area of pharmaceutical industry [1]. Nowadays, more than 150 peptides and proteins have been approved by Food and Drug Administration of USA as therapeutic agents for the prevention, diagnosis and/or treatment of different kinds of diseases and there are more than 900 protein-based drugs in different phases of clinical trials [2]; among them 39 monoclonal antibodies (mAbs) are in the late stages of phase 3 studies and it is anticipated that 4 mAbs will be submitted for marketing application by the end of 2015 [3].

Biopharmaceuticals are large molecules with an inherent physicochemical complexity. It is obvious that, such complex molecules with a variety of functional groups are susceptible to instability through different degradation pathways that could happen as a result of exposure to different environmental changes and stresses during their multistep production procedure, handling, shipping, storage and even after administration to patients. Although, instability of biopharmaceuticals could impair their efficacy and potency, the most important concern about their instability is related to the presence of degradation products as a major risk factor in the immunogenicity of formulated therapeutics. Therefore, stability studies are one of the most crucial parts of quality control of biopharmaceuticals [4,5].

Stability of biopharmaceuticals could be categorized as physical and chemical stabilities. Physical instability of biopharmaceuticals is related to the changes in their higher order structures. It covers

Abbreviations: BPTI, bovine pancreatic trypsin inhibitor; CDR, complementarity determining region; CE, capillary electrophoresis; CZE, capillary zone electrophoresis; DKP, diketopiperazine; DTT, dithiothreitol; Fab, antigen binding fragment of a monoclonal antibody; Fc, fragment crystallizable; ICH, international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use; INF-α, interferon-alpha; h, hour/hours; HPLC, high performance liquid chromatography; hPTH, human parathyroid hormone; mAb, monoclonal antibody; min, minute/minutes; MS, mass spectroscopy; PGA, pyroglutamic acid; rhGH, recombinant human growth hormone; rhIL, recombinant human interleukin; rh-GM-CSF, recombinant human granulocyte-macrophage colony-stimulating factor; rhPTH, recombinant human parathyroid hormone; rpm, rounds per minute; SDS, sodium dodecyl sulfate; SIMs, stability indicating methods; tBHP, *tert*-butyl hydroperoxide.

* Corresponding author. Tel.: +98 41 33379323; fax: +98 41 33363231.
E-mail address: ajouyban@hotmail.com (A. Jouyban).

http://dx.doi.org/10.1016/j.ejpb.2015.10.016
0939-6411/© 2015 Elsevier B.V. All rights reserved.

thermal and conformational instabilities as well, which are considered as alterations in optimal transition point (unfolding temperature) and native three dimensional globular structures of proteins, respectively. Physical instability could occur due to different degradation events such as unfolding, dissociation, denaturation, adsorption, aggregation and precipitation [6–8]; for instance, protein unfolding is an important physical instability which could disturb tertiary and frequently secondary structure of proteins; this conformational alteration could impair biological activity of biopharmaceuticals and could induce irreversible protein aggregation [9], while chemical instability is associated with formation and/or breakage of covalent bonds in the first order structure of biopharmaceuticals and could be triggered by different degradation pathways such as oxidation, reduction, deamidation, hydrolysis, arginine conversion, β-elimination, racemization and disulfide exchange [6,7].

It should be considered that, although, physical and chemical stabilities are required for the biological activity of biopharmaceuticals, they could not assure their potency and safety. Hence, to provide complete stability profile of biopharmaceuticals, in addition to physical and chemical stabilities, biological stability, which represents the stability of biopharmaceuticals against any alteration in biological activity, potency, toxicity and immunogenicity under the influence of different environmental factors, should be evaluated using appropriate techniques [10,11].

Over and above the real time–real condition stability studies that are applied to specify expiry date and suitable storage and handling conditions of biopharmaceutical products, stability studies under stress conditions or forced degradation studies are also important.

As it is shown in Fig. 1, the obtained results from these studies could be utilized for determination of intrinsic stability of drug substances, selection of biopharmaceutical candidates, early formulation developments and comparability studies, generating degradation profile of pharmaceutical active ingredients and finished products, identification of degradation products and elucidation of their structures, investigation of the degradation mechanisms and pathways and selection of possible stabilizers to block these pathways [12–14], as well as, development of stability indicating methods (SIMs) [15,16].

Moreover, forced degradation studies could be driven to simulate accidental exposure of biopharmaceuticals to unrecommended conditions during their production, storage, handling and administration; these studies could indicate performance of bioassay techniques for potency testing of biopharmaceuticals and could provide useful information about the possible effect of certain degradation products on toxicity and immunogenicity of biopharmaceutical formulations [12–14].

To conduct forced degradation studies, in addition to the reliable analytical tools required to track all potential degradation mechanisms, there is an inevitable demand to choose desirable

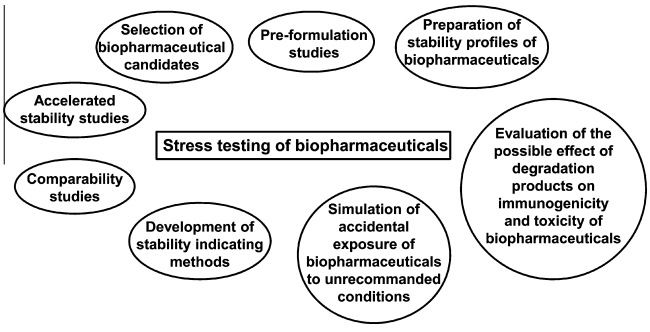

Fig. 1. Role of stress testing in different areas of biopharmaceutical industry.

stress conditions based on tendencies of biopharmaceuticals to instability through different pathways. Along with stress type, timing of stress testing and extent of degradation needed to attain or degradation limit should be wisely selected to achieve more realistic degradation pathways, as over-stressing could lead to extreme degradation and could trigger formation of secondary degradation products that may not produce during real time–real condition and/or accelerated stability studies and under-stressing might result in inadequate degradation [14,17]. Regarding small molecule compounds, it is recommended that oxidative and other stresses should be applied for up to 24 h and 14 days, respectively, to achieve degradation extent of 5–20% that is sufficient for development of SIMs [14].

International conference on harmonisation (ICH) of technical requirements for registration of pharmaceuticals for human use makes some guidelines available for stability studies; ICH Q1A (R2) guidelines [18] represent some general recommendations about forced degradation studies of pharmaceutical substances and products and ICH Q1B guidelines [19] provide some instructions regarding applicable light sources and regulation of light exposure levels in photo-stability testing of new drug substances and products. Additionally, American Society for Testing Materials guidelines on vibration testing of shipping containers [20] advise some general commands that could be utilized to stimulate shipping induced mechanical stress.

However, in the case of biotechnological and biological products, ICH Q5C guidelines [10] only recommend that stress conditions "should be selected on case by case bases" and there is neither practical protocol available to set up stress testing of biopharmaceuticals nor well-established acceptance criteria to interpret the obtained results from stress studies [21]. Therefore, the responsibility of such a demanding and tricky task has been fallen on the shoulders of researchers and manufacturers involved in biopharmaceutical industry. So that, biopharmaceutical companies should have some in-house instructions for selecting suitable and the most relevant stress conditions and timing of stress testing to avoid over and under-stressing.

Review of the literature revealed that there are some articles dealing with the analytical tools used to study degradation of therapeutic peptides, proteins and vaccines [5,7,21], and there is a review covering forced degradation of therapeutic proteins and discussing different approaches employed for forced degradation studies in different phases of their development [22]. Besides, some case studies about candidate selection, comparability studies and photo-stability have been reported as a part of the project approved by Biomanufacturing Working Group of European Biopharmaceutical Enterprising to "provide industry best practice for the forced degradation studies of therapeutic proteins based on the experiences of European Biopharmaceutical Enterprising member companies" [23]. Nevertheless, there is no practical outline about the applied stress conditions in forced degradation and/or stress testing of biopharmaceuticals.

Since stability guidelines are leaking and selection of stress conditions is rather difficult, it is the main objective of the present review to provide convenient information about stress conditions applicable to forced degradation studies of biopharmaceuticals in both active ingredients and finished products.

It should be declared that literature search has been carried out by searching electronically data sources to find stress conditions employed to induce physical and/or chemical instabilities of biopharmaceuticals using some keywords including biopharmaceutical, stress conditions, forced degradation, chemical stability and physical stability. Moreover, stress conditions applied for forced degradation of heparin are included, as heparin is one of the first biopolymeric drugs with a complex biologically derived carbohydrate structure [24] and according to the broad biotechnology

Download English Version:

https://daneshyari.com/en/article/2083263

Download Persian Version:

https://daneshyari.com/article/2083263

Daneshyari.com