Journal of Pharmaceutical and Biomedical Analysis 48 (2008) 744–748

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

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

The impact of primary packaging on the quality of parenteral products

Ljiljana Solomun[a], Svetlana Ibric[b,*], Zorana Boltic[a], Zorica Djuric[b], Biljana Stupar[a]

[a] Hemofarm A.D. Vrsac, Serbia
[b] Department of Pharmaceutical Technology, Institute of Pharmaceutical Technology, Faculty of Pharmacy, Vojvode Stepe 450, 11221 Belgrade, Serbia

ARTICLE INFO

Article history:
Received 29 February 2008
Received in revised form 20 July 2008
Accepted 21 July 2008
Available online 8 August 2008

Keywords:
Dual chamber vials
Rubber closures formulation
Methylprednisolone sodium succinate
Injection

ABSTRACT

The unique approach in manufacturing of pharmaceutical dosage forms of active substances known to be unstable in aqueous solution is the introduction of lyophilization process. Nevertheless, these products must be reconstituted using the diluent from a separate container before application. The possible solution for this problem is the application of dual chamber vials comprising the freeze-dried product in a lower compartment of the vial and the solution for reconstitution in the upper chamber. The main issue in development of such product is the choice of contact packaging (rubber closures, glass vials and the container closure system as a whole). The most important parameter used for evaluation of the influence of contact material on product quality was the pH value. The results have shown that the type of vials (moulded or tubular glass) has no impact on pH shift of the solution for reconstitution (tested solution—TS), while significant differences in pH value of the TS were observed depending on the rubber closures formulation used (with some formulations, the pH shift during the test was 6.5–9.14). Benzyl alcohol assay during the tests remained unchanged. Integrity tests of the container closure system (CCS) have demonstrated the adequacy of the selected packaging system. The quality of the CCS of choice was confirmed in the course of stability studies, only parameters directly influenced by CCS being presented in this work: loss on drying and pH value. On the basis of these results, no changes in loss on drying were connected to CCS, and the pH value of the reconstituted solution remains unchanged in samples tested both ex-tempore and after in-use period of 48 h.

1. Introduction

New pharmaceutical dosage forms, as well as new delivery systems are more and more subject of development processes and focus of the pharmaceutical industry, beside the introduction of new pharmacological active substances. This is especially true for the variety of well-known substances which are in use for many years and connected with different problems related to existing, conventional, pharmaceutical dosage forms. Because of the limited stability in the presence of moisture, for some active substances it is necessary to use the lyophilization process in order to achieve long-term stability. Problems associated with this type of injections are complicated because the medication to be administered must be stored as two separate component parts and then mixed, prior to injection. This mostly applies to the risk of microbiological contamination, spilling during preparation, safety of medical personnel, time consuming application and often need for urgent use of these drugs. Therefore, dual chamber vials have been developed to facilitate storage and mixing of such two-component medications. This new type of primary packaging system enables safe, easy and fast preparation of medicines for application.

The biggest problem during development of such products [1], i.e., injections in dual chamber vials, is the choice of contact packaging materials and evaluation of their impact on the drug product quality, both initially and during its estimated shelf life. Thus, the goal of this work is to demonstrate the procedure and the relevant results used in order to choose an optimal solution for the container closure system of this type.

The package consists of the dual chamber glass vial with two types of rubber closures and the plastic cap. The lyophilized powder in the lower chamber is separated from the diluent in the upper chamber by the intermediate rubber closure. The upper chamber is closed by another rubber closure and the plastic cap on top (Fig. 1).

Different chemical, physical and microbiological analysis were performed in order to estimate the influence of the glass type, rubber formulation and the container closure system as a whole (package integrity) on product quality. Since polypropylene plastic cap is not a part of contact packaging it was not considered critical in this study.

* Corresponding author. Tel.: +381 11 3972840.
E-mail address: ibric@beotel.net (S. Ibric).

0731-7085/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jpba.2008.07.025

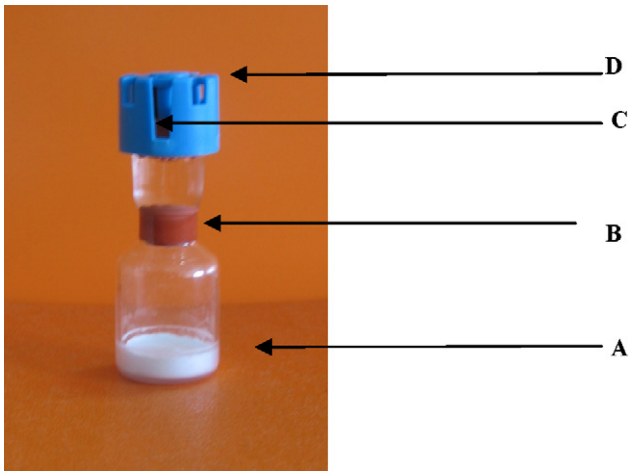

Fig. 1. Container closure system—A: dual chamber vial; B: intermediate closure; C: upper closure; D: plastic cap (plastic activator).

Table 1
Storage conditions for integrity testing

Sample No.	Conditioning temperature (°C)	Time (months)
1	5	3
2	5	6
3	50	2
4	60	1

Table 2
Storage conditions and testing frequencies

Storage conditions		Storage orientation	Testing time points (months)
Accelerated	40 ± 2 °C/75 ± 5% RH	Horizontal	0, 1, 2, 3 and 6
		Upright	0, 3 and 6
Intermediate	30 ± 2 °C/65 ± 5% RH	Horizontal	0, 3, 6, 9 and 12
		Upright	0, 6 and 12
Long-term	25 ± 2 °C/60 ± 5% RH	Horizontal	0, 3, 6, 9, 12, 18, 24, 36, 48 and 60
		Upright	0, 12, 24, 36, 48 and 60

2. Experimental

2.1. Model drug

Methylprednisolone sodium succinate [2] lyophilisate for injection was used as a model drug and water for injection with 0.9% benzyl alcohol as diluent—test solution (TS). Benzyl alcohol as preservation agent was used in the solution for reconstitution, because the reconstituted solution has to be unchanged after in-use period of 48 h.

2.2. Vials

Dual chamber vials are made of Type I borosilicate glass [3]. In order to evaluate the influence of the vials on pH shift, vials made of moulded glass (Saint Gobain) and tubular glass (Schoott) were used. TS (5 ml) was placed in the lower chamber of tested vials and stored at different temperatures/RH during 5 days. Both glass vials were Type I glass containers: neutral glass, with a high hydrolytic resistance due to the chemical composition of the glass itself. It was needlessly to carry out test longer, because test for hydrolytic resistance was also carried out to control hydrolytic resistance of glass vials.

Table 4
pH values of the TS in two types of glass vials under different storage conditions

Storage conditions	Tubular glass	Moulded glass
40 °C/75% RH	6.50	6.36
30 °C/65% RH	6.54	6.08
25 °C/60% RH	6.40	6.07

Table 5
Benzyl alcohol assay (% of declared value) in TS after conditioning 4 weeks

Rubber formulation	Initially	7 days	14 days	21 days	28 days
F1	99.5	99.3	98.1	98.4	97.2
F2	99.7	100.7	101.2	99.5	100.2
F3	100.1	99.3	99.1	100.2	98.4
F4	99.0	100.2	98.3	99.4	98.3
F5	99.3	98.2	100.2	100.5	99.4
F6	99.5	100.2	98.3	100.1	98.6

2.3. Rubber closures

Considering the specific nature of the packaging system, where diluent is constantly in contact with both rubber closures made of the same rubber formulation, this part of the packaging system is most critical in terms of compatibility. Experiments were performed using six different rubber formulations (chloro and bromobutyl compounds): bromobutyl compound for wide-range application Type I (F1), bromobutyl compound for wide-range application Type II (F2), bromobutyl compound for wide-range application Type III (F3), standard chlorobutyl compound (F4), low moisture bromobutyl compound (F5) and ultra-low extractables bromobutyl compound (F6).

2.3.1. Immersion experiments

I Test: Rubber closures (external surface of 50 cm^2) were immersed in 50 ml of TS and stored at 40 °C for 4 weeks. Benzyl alcohol assay and pH measurements were performed in predetermined time intervals.
II Test: Rubber closures (intermediate closures and upper closures) were immersed in TS, autoclaved at 121 °C for 30 min and stored at 25 °C/60%RH for 2 weeks. Benzyl alcohol assay and pH measurements were performed initially and after 2-week period.

2.4. Package integrity

For microbiological attributes, packaging integrity is important in the sense of maintaining the sterility of the product during shelf life. Integrity testing was performed in two stages: (I) in accordance with USP [4] <1207> sterile product packaging—integrity

Table 3
Testing points for in-use stability evaluation

	40 °C/75% RH		30 °C/65% RH		25 °C/60% RH			
Sample/time (months)	0	6	0	12	0	12	24	60