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

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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.

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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.

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doi:10.1016/j.jpba.2008.07.025

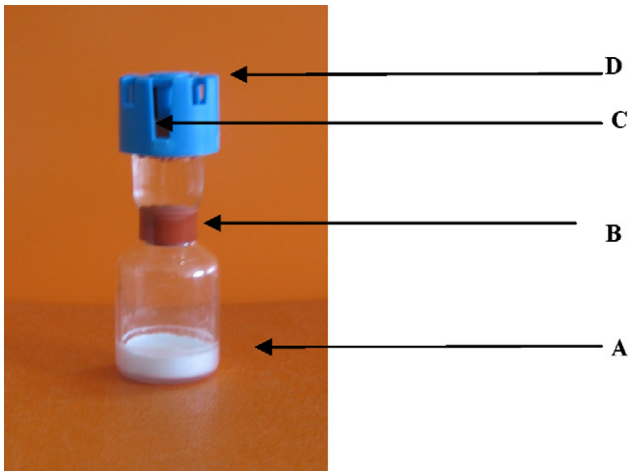

Fig. 1. Container closure system—A: dual chamber vial; B: intermediate closure; C: upper closure; D: plastic cap (plastic activator).

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

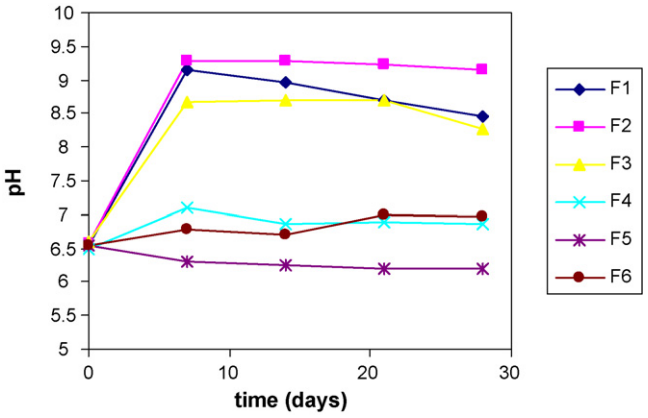

Fig. 2. pH shift of TS with different rubber formulations.

evaluation and (II) "challenge test", using the same packaging system.

2.4.1. Integrity testing according to USP

The USP chapter <1207> relates to the application of physical and microbiological tests for container closure integrity during the development phase. The samples were tested for initial integrity, but also after storage under various conditions (given in Table 1) which simulate temperature excursions during shipment.

Physical testing: Physical testing was performed using the method and test conditions described in ISO 8871-5 Annex D (August, 2005) in combination with ASTM F2338-05.
Microbiological testing: From microbiological point of view, only the upper part of the vial is considered critical in terms of potential contamination. The test was performed in accordance with USP 28-NF 23, 2005: <71> sterility.

2.4.2. "Challenge test"

This test was performed in accordance with GMP requirements for sterile production [3].

2.5. Stability testing

One of the most important requirements for pharmaceutical products is to keep all defined parameters during its shelf life. So, stability tests have been carried out in accordance with the current ICH guidances [5–10].

The batch used in the stability study was fully representative of the planned commercial drug product. It was manufactured according to the intended commercial formulation using the container closure system proposed for the marketed product and the batch size is production scale.

The storage conditions and length of study was chosen to support the recommended long-term storage condition and conditions of use. Stability testing of the drug product after reconstitution was conducted as well.

The design of the formal ICH-compliant stability studies encompass the storage conditions and testing frequencies outlined in Table 2. During the stability study, the vials were kept in horizontal, as well as, in upright position. Horizontal position was chosen, for compatibility assessment, in other words to assure maximal contact of diluent of the subject drug product with rubber closures.

Some of tested parameters could be directly influenced by container closure system and therefore will be pointed out.

2.5.1. pH of reconstituted solution

Lyo-cake was reconstituted by pushing diluent into the lower chamber. pH value was measured immediately after reconstitution.

2.5.2. Loss on drying

This test was performed in accordance with Ph. Eur 2.2.32.

2.6. "In-use" compatibility

"In-use" compatibility was also considered critical, since intermediate elastomeric closure is in contact with reconstituted product during the 48 h period. In order to establish the quality requirements, potential leachables were taken into account. This was based on the extraction study for the selected rubber formulation, performed by manufacturer of the elastomeric closures. "In-use" compatibility was assessed in the course of the stability study using container closure system defined as an optimal solution in terms of chemical and physical characteristics as well as the required functionality.

"In-use" stability/compatibility testing of the drug product was performed according to ICH guidances [11,12].

"In-use" stability/compatibility testing is being evaluated by examining quality parameters of the subject drug product susceptible to change at the end of the proposed "in-use" shelf life (i.e., at 48 h after reconstitution). The lyophilized product was reconstituted utilizing the water for injection with 0.9% benzyl alcohol provided in the upper chamber of the vial. Samples were tested inicially as well on the end of testing period, design is presented in Table 3.

3. Results and discussion

Influence of glass vials type in terms of pH shift of the TS after 5 days is given in Table 4.

Obtained results indicate that there are no changes in pH value of the TS. Nevertheless, tubular glass was chosen for further evaluation of the container closure system due to its better performance during the lyophilization process in which the thickness of the vial bottom is an important parameter.

After immersion of different rubber closures (different formulations) in the TS (Test I), were obtain results (pH and benzyl alcohol assay) presented in Fig. 2.

Furthermore, assay of benzyl alcohol in the TS with different rubber closures is presented in Table 5.

It is obvious that the increase in pH value is most significant when formulation F2 is used (from 6.5 to 9.14), while with

Table 6
Results for Test II

	pH values of TS		Benzyl Alcohol Assay (% of declared value)	
	Initially	14 days	Initially	14 days
TS (blank)	6.92	6.51	99.7	98.6
Intermediate closures	7.11	6.96	99.5	100.4
Upper closures	7.31	7.22	99.0	99.8

Table 7
Results for pH value measured immediately after reconstitution of vials kept in upright (A) and horizontal (B) position

Conditions	Storage interval (months)[a]							
	1	2	3	6	9	12	18	24
A—vials kept in upright position								
40 °C/75% RH	7.50	7.60	7.51	7.53				
30 °C/65% RH			7.48	7.56	7.41	7.52		
25 °C/60% RH			7.50	7.56	7.48	7.53	7.54	7.42

Conditions	Storage interval (months)[a]				
	3	6	12	18	24
B—vials kept in horizontal position					
40 °C/75% RH	7.38	7.55			
30 °C/65% RH	7.59	7.60	7.60		
25 °C/60% RH			7.50	7.62	7.56

Note: initial value was 7.58.
[a] Test is in the progress.

Table 8
Results for loss on drying—samples conditioned at different temperatures

Conditions	Storage interval (months)[a]							
	1	2	3	6	9	12	18	24
A—vials kept in upright position								
40 °C/75% RH	0.85	0.70	0.65	0.96				
30 °C/65% RH			0.76	0.77	0.32	0.98		
25 °C/60% RH			0.47	0.72	0.40	0.97	0.50	0.89

Conditions	Storage interval (months)[a]				
	3	6	12	18	24
B—vials kept in horizontal position					
40 °C/75% RH	0.29	0.45			
30 °C/65% RH		0.31	0.70		
25 °C/60% RH			0.60	0.75	0.67

Note: initial value was 0.31.
[a] Test is in the progress.

formulation F5 (low moisture bromobutyl compound) decrease of pH value was noticed. It was also observed that experiments with formulations F4 and F6 (chlorobutyl compound and ultra-low extractables bromobutyl compound, respectively) resulted in no significant change of the pH value.

There are no statistically significant changes in assay of benzyl alcohol during the test, meaning there is no influence of rubber formulation on this parameter.

Nevertheless, not only chemical characteristics should be taken into consideration when it comes to rubber closures. Having in mind their specific functionality within the packaging system of dual chamber vials, care should be taken in terms of rubber closures' physical characteristics and features of the intermediate closure to avoid moisture transition from the upper chamber to the lower compartment with lyophilized cake during storage. Additionally, during the application of the drug product, intermediate closure has to move under pressure into the lower chamber. Therefore, F3 was selected for further testing, due to better functionality of closures made of this formulation. The increase of pH value was compensated by adding the buffer compound into the solution for lyophilization.

Table 9
Results for pH value during in-use testing at final test points—pH values

	Final result—upright position	Final result—horizontal position
40 °C/75% RH	7.53	7.44
30 °C/65% RH	7.42	7.40
25 °C/60% RH	7.46	7.40

Test II was performed using formulation F3 (bromobutyl compound for wide-range application, Type III) and the results are summarized in Table 6 (pH shift of the TS and benzyl alcohol assay).

On the basis of the results presented in Table 6, there is no change in pH value during the test. The differences are only obvious initially, depending on the surface which is in contact with the solution.

Integrity testing was performed in order to confirm the suitability of the selected packaging system. On the basis of the results obtained using both physical and microbiological method during development, the integrity of the proposed container closure system was confirmed.

Accelerated, intermediate and long-term stability, as well as in-use stability tests were performed. A systematic approach was applied to the evaluation of stability information [13] gathered over stability study that evaluated physical, chemical and microbiological quality characteristics. Results of relevant parameters (pH value and loss on drying) obtained during stability testing are presented in Tables 7 and 8.

No changes in pH were observed during conditioning, neither the influence of the different position of the vials.

Loss on drying varies in different vials. Nevertheless, no increasing trend was observed during stability testing, and the differences in tested parameter could be due to the lyophilization process itself. Values for loss on drying varied between vials depending on position of vial in the tunnel during lyophilization process.

"In-use" compatibility was assessed with the chosen elements of the container closure system. Since pH was evaluated within tests performed in order to evaluate chemical influence of the contact packaging on product quality, and the potential shift was observed, this parameter will be taken into consideration during in-use stability assessment.

pH values measured 48 h after reconstitution of the samples at final test points are presented in Table 9.

There are no statistically significant changes in pH value during the test.

4. Conclusion

Container closure system described in this article is predicted to enable easier, faster and more comfortable administration. In the course of this study, it was confirmed that the selection of rubber closures formulation represents the main issue in terms of compatibility and the overall impact of the contact packaging (materials and design) was evaluated. According to the integrity testing results, as well as the results of the stability study obtained using the selected container closure system, it was verified that it provides an appropriate protection for the drug product which quality was preserved during the estimated shelf life. Furthermore, "in-use" stability testing indicated no compatibility issues with the rubber formulation of choice.

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